National Guideline Centre

Final version

Asthma

Asthma: diagnosis and monitoring of asthma in adults, children and young people

NICE guideline NG80

Appendices A - R

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Appendices

Appendix A: Scope

FINAL SCOPE

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SCOPE

1 Guideline title

Asthma: diagnosis and monitoring of asthma in adults, children and young people

1.1 Short title

Asthma: diagnosis and monitoring

2 The remit

The Department of Health has asked NICE: 'to prepare a guideline on the diagnosis and management of asthma'.

3 Clinical need for the guideline

3.1 Epidemiology

a) Asthma is a chronic inflammatory respiratory disease that can affect people of any age but often starts in childhood. It is characterised by attacks of breathlessness and wheezing, with the severity and frequency of attacks varying from person to person. The attacks are associated with variable airflow obstruction within the lung, which is often reversible with or without treatment.

b) The World Health Organization estimates that worldwide 235 million people suffer from asthma and that it is the most common chronic condition affecting children. In the UK 5.4 million people are receiving treatment for asthma, including 1.1 million children.

c) Studies of adults diagnosed with asthma suggest that up to 30% do not have clear evidence of asthma. Some may have had asthma in

the past, but it is likely that many have been given an incorrect diagnosis.

d) The causes of asthma are not well understood. A combination of risk factors is associated with the condition. Risk factors include both genetic (the condition clusters in families) and environmental (such as inhalation of allergens or chemical irritants) influences. Occupational causes of asthma in adults are often unrecognised.

3.2 Current practice

a) Asthma is diagnosed principally on the basis of a careful history taken by an experienced clinician. Initial clinical assessment includes questions about symptoms (wheezing, cough, breathing and chest problems) and any personal or family history of allergies, atopic disorders or asthma. Various tests can be used to support a diagnosis, but there is no single test that serves as a gold standard.

b) A number of methods and assessments are available to determine the likelihood of asthma. These include measures of airflow obstruction (spirometry and peak flow) and measures of reversibility with bronchodilators, both of which are widely used in current practice. However, normal results do not exclude asthma and abnormal results could be indicators of other respiratory diseases.

c) Testing for airway inflammation is increasingly used as a diagnostic strategy in clinical practice. This includes measuring sputum eosinophil counts and fractional exhaled nitric oxide (FeNO). However, there is some uncertainty about both the sensitivity and specificity of FeNO, particularly whether it can distinguish general atopy from asthma.

d) Other diagnostic strategies include blood or skin prick tests to detect allergic reactions to environmental influences, exercise tests to detect evidence of bronchoconstriction, and measures of airway

hyper-reactivity, such as histamine/methacholine PC20 and mannitol challenge. However, it is debatable which test or measure, or combination- of them, is the most effective to accurately diagnose asthma.

e) It is recognised that asthma control is suboptimal in many people with asthma. This has an impact on their quality of life, their use of healthcare services and the associated costs. Asthma control can be monitored by measuring airway inflammation and by using validated questionnaires, but the most effective monitoring strategy is uncertain.

4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider.

It is based on the referral from the Department of Health, but now covers the diagnosis and monitoring of asthma and excludes other aspects of management. This is because there is evidence that incorrect diagnosis is a significant problem whereas management of correctly diagnosed asthma is straightforward in most cases. Also, NICE technology appraisal guidance covers some of the available asthma therapies. In the future NICE will consider whether further guidance on asthma covering the aspects omitted from the current scope is needed.

The areas that will be addressed by the current guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a) Adults, children and young people who are being investigated for suspected asthma, or who have been diagnosed with asthma and are having their condition monitored.

b) Specific consideration will be given to subgroups based on age, broadly divided into younger children, older children, and older people (aged over 75 years).

4.2 Healthcare setting

a) Primary, secondary and community care settings in which NHS-funded care is provided.

4.3 Diagnosis and monitoring

4.3.1 Key clinical issues that will be covered

Diagnosis

Initial clinical assessment

a) The value of specific signs and symptoms in making a diagnosis of asthma. For example, wheezing, cough, breathlessness and other respiratory symptoms including diurnal and seasonal variations; symptoms in response to exercise; and symptoms after taking drugs such as aspirin, other non-steroidal anti-inflammatory drugs and beta-blockers.

b) The value of a family or personal history of atopic disorders in making a diagnosis of asthma.

c) Case identification of occupational asthma.

Objective tests

The value of the following tests in making a diagnosis of asthma:

d) Measures of lung function and airway obstruction including spirometry/flow volume loop, peak expiratory flow (PEF) variability,

bronchodilator response (using PEF or forced expiratory volume in 1 second), and measures of airway hyper-reactivity, such as histamine/methacholine PC20 and mannitol challenge.

e) Biomarkers of airway inflammation and allergy: skin tests for the common aero-allergens, serum total IgE, peripheral blood eosinophil count and FeNO.

f) Measures of exercise-induced bronchoconstriction.

Monitoring

g) Assessment of asthma control using self- or parental reports such as symptom scores or diaries, and validated asthma control questionnaires such as the asthma control test (ACT), the children's asthma control test (CACT), the asthma control questionnaire-7 (ACQ-7), and the Royal College of Physicians 3 (RCP3) questions.

h) Use of tele-healthcare as a route for assessment.

i) Monitoring adherence.

j) Inhaler technique.

k) Assessment of asthma control using tests such as measures of pulmonary function (for example, spirometry and peak expiratory flow meters) and measures of airway hyper-reactivity.

l) Assessments of asthma control using tests or measures such as FeNO.

4.3.2 Clinical issues that will not be covered

a) Tertiary care setting.

b) Severe, difficult to control asthma.

c) Sputum cell counts.

d) Treating asthma.

4.4 Main outcomes

a) Objective response to treatment.

b) Accuracy of diagnostic tests.

c) Frequency of asthma attacks.

d) Need for oral corticosteroids and short-acting beta-agonists.

e) Unscheduled use of healthcare services.

f) Health-related quality of life.

g) Time off school or work.

4.5 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually only be from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see 'Further information').

4.6 Status

4.6.1 Scope

This is the final version of the scope.

4.6.2 Timing

The development of the guideline recommendations will begin in August 2013.

5 Related NICE guidance

5.1 Published guidance and quality standards

- Omalizumab for the treatment of severe persistent allergic asthma in children aged 6 and over and adults (review of TA133 and TA201) NICE technology appraisal guidance TA278 (2013).
- Quality standard for asthma. NICE quality standard 25 (2013).
- Bronchial thermoplasty for severe asthma. NICE interventional procedure guidance 419 (2012).
- Roflumilast for the management of severe chronic obstructive pulmonary disease. NICE technology appraisal guidance 244 (2012).
- Chronic obstructive pulmonary disease (updated). NICE clinical guideline 101 (2009).
- Respiratory tract infections. NICE clinical guideline 69 (2008).
- Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over. NICE technology appraisal guidance 138 (2008).
- Inhaled corticosteroids for the treatment of chronic asthma in children under the age of 12 years. NICE technology appraisal guidance 131 (2007).
- Inhaler devices for routine treatment of chronic asthma in older children (aged 5–15 years). NICE technology appraisal guidance 38 (2002).
- Guidance on the use of inhaler systems (devices) in children under the age of 5 years with chronic asthma. NICE technology appraisal guidance 10 (2000).

5.2 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website).

- Measuring fractional exhaled nitric oxide concentration in asthma – NIOX MINO, NIOX VERO and NObreath. NICE diagnostic assessment programme. Publication expected April 2014.

- Bronchiolitis: diagnosis and management of bronchiolitis in children. NICE clinical guideline. Publication expected April 2015.

6 Further information

Information on the guideline development process is provided in the following documents, available from the NICE website:

- How NICE clinical guidelines are developed: an overview for stakeholders' the public and the NHS
- The guidelines manual.

Information on the progress of the guideline will also be available from the NICE website.

Appendix B: Declarations of interest

The 2007 version of the NICE code of practice for declaring and dealing with conflicts of interest policy was applied to this guideline.

Andrew Menzies-Gow (GC Chair)

Date	Item declared	Classification	Action taken
GC1 (29.7.13)	Received payment for attending advisory boards for Roche, NAPP, Boehringer Ingelheim and Novartis. Received lecture fees for presenting and chairing education meetings from Novartis, Glaxo SmithKline and NAPP. Royal Brompton and Harefield NHS Foundation Trust received payment from Glaxo SmithKline, Novartis and Roche for participation in phase II and III studies on severe asthma where Andrew Menzies-Gow is the principal investigator. Holds one current grant from Asthma UK. Member of the BTS severe asthma network and BTS asthma SAG. Andrew Menzies-Gow resigned position on the BTS/SIGN asthma guidelines.	Non-specific personal pecuniary Non-specific non-personal pecuniary – (monitoring questionnaires review) ACT and CACT developed by GSK but both are freely available (non-profit making). Personal non-pecuniary	Declare and participate Declare and participate Declare and participate
GC2 (3.9.13)	Received payment for advisory board attendance for Amgen who are trialling a novel monoclonal antibody for use in severe asthma, October 2013.	Non-specific personal pecuniary	Declare and participate
GC3 (8.10.13)	No change to existing declarations.	n/a	n/a
GC4 (19.11.13)	No change to existing declarations.	n/a	n/a
GC5&6 (27.1.14 & 28.1.14)	Attended advisory boards for Roche on Lebrikizumab in severe asthma, January and February 2014.	Non-specific personal pecuniary	Declare and participate
GC7 (3.3.14)	Presented on specialist commissioning of severe asthma at 4 meetings for Novartis.	Non-specific personal pecuniary	Declare and participate

Date	Item declared	Classification	Action taken
	Presented at 2 meetings in Denmark on severe asthma for Novartis. Attended Gulf Thoracic Society in UAE, sponsored by Novartis.		
GC8 (8.4.14)	No change to existing declarations.	n/a	n/a
GC9 (13.5.14)	Two presentations to primary care on the use of Flutiform in asthma, sponsored by NAPP. One presentation on specialist commissioning of severe asthma services sponsored by Novartis.	Non-specific personal pecuniary	Declare and participate
GC10 (16.6.14)	No change to existing declarations.	n/a	n/a
GC11 (22.7.14)	Attended one advisory board for Boehringer Ingelheim discussing the use of Tiotropium in severe asthma. Received lecture fees from NAPP for talking about the use of Flutiform in asthma. Received lecture fees from Glaxo SmithKline for talking about Real Life clinical trials and the Salford Lung Study Received lecture fees from Chiesi for talking about the Management of Severe Asthma	Non-specific personal pecuniary Non-specific personal pecuniary Non-specific personal pecuniary Non-specific personal pecuniary	Declare and participate
GC12 (2.9.14)	Filmed for Boehringer Ingelheim on the use of Tiotropium in severe asthma.	Non-specific personal pecuniary	Declare and participate
GC13 (7.10.14)	Lecture fees for a presentation on severe asthma for Boehringer Ingelheim Lecture fees for a pro con debate on severe asthma for Novartis Lecture fees for a presentation on treatment options for severe asthma and severe asthma workshop for severe asthma for Boehringer-Ingelheim	Non-specific personal pecuniary	Declare and participate
GC14 (30.3.15)	Received speaker fees from Glaxo SmithKline, Novartis, Astra Zeneca and Boehringer Ingelheim for speaking about new treatment options for asthma. Attended an advisory board for Roche discussing novel therapies for severe asthma	Non-specific personal pecuniary	Declare and participate
GC15 (9.5.17)	Attended advisory boards and or received lecture fees from: Astra Zeneca, Glaxo SmithKline, Teva, Napp, Mundi Pharma, Novartis, Boehringer Ingelheim, Vectura and Hoffman La Roche.	Non-specific personal pecuniary	Declare and participate

Date	Item declared	Classification	Action taken
	Attended international conferences with Napp and Boehringer Ingelheim. Participated in clinical studies for which my institution has been reimbursed with Glaxo SmithKline, Hoffman La Roche and Boehringer Ingelheim. Consultancy agreements with Astra Zeneca and Vectura.		
GC16 (15.8.17)	No change to existing declarations.	n/a	n/a

John Alexander

Date	Item declared	Classification	Action taken
GC1 (29.7.13)	None	n/a	n/a
GC2 (3.9.13)	No change to existing declarations.	n/a	n/a
GC3 (8.10.13)	No change to existing declarations.	n/a	n/a
GC4 (19.11.13)	No change to existing declarations.	n/a	n/a
GC5&6 (27.1.14 & 28.1.14)	Received lecture fee from GSK for lecture to GPs.	Non-specific personal pecuniary – (monitoring questionnaires review) ACT and CACT developed by GSK but both are freely available (non-profit making).	Declare and participate
GC7 (3.3.14)	No change to existing declarations.	n/a	n/a
GC8 (8.4.14)	No change to existing declarations.	n/a	n/a
GC9 (13.5.14)	No change to existing declarations.	n/a	n/a
GC10 (16.6.14)	No change to existing declarations.	n/a	n/a
GC11 (22.7.14)	Paid lecture on RSV for Abbvie. Paid advisory board on preventing RSV admissions by Abbvie.	Non-specific personal pecuniary Non-specific personal pecuniary	Declare and participate
GC12 (2.9.14)	No change to existing declarations.	n/a	n/a

Date	Item declared	Classification	Action taken
GC13 (7.10.14)	No change to existing declarations.	n/a	n/a
GC14 (30.3.15)	No change to existing declarations.	n/a	n/a
GC15 (9.5.17)	No change to existing declarations.	n/a	n/a
GC16 (15.8.17)	No change to existing declarations.	n/a	n/a

Tara Burn

Date	Item declared	Classification	Action taken
GC1 (29.7.13)	None	n/a	n/a
GC2 (3.9.13)	No change to existing declarations.	n/a	n/a
GC3 (8.10.13)	No change to existing declarations.	n/a	n/a
GC4 (19.11.13)	No change to existing declarations.	n/a	n/a
GC5&6 (27.1.14 & 28.1.14)	No change to existing declarations.	n/a	n/a
GC7 (3.3.14)	No change to existing declarations.	n/a	n/a
GC8 (8.4.14)	No change to existing declarations.	n/a	n/a
GC9 (13.5.14)	No change to existing declarations.	n/a	n/a
GC10 (16.6.14)	No change to existing declarations.	n/a	n/a
GC11 (22.7.14)	No change to existing declarations.	n/a	n/a
GC12 (2.9.14)	No change to existing declarations.	n/a	n/a
GC13 (7.10.14)	No change to existing declarations.	n/a	n/a
GC14 (30.3.15)	No change to existing declarations.	n/a	n/a
GC15 (9.5.17)	Did not participate.	n/a	n/a
GC16 (15.8.17)	Did not participate.	n/a	n/a

Erol Gaillard

Date	Item declared	Classification	Action taken
GC1 (29.7.13)	One research grant for £3000 from Novartis. Newly appointed member to the SIGN/BTS Asthma Guideline Development Group.	Non-personal pecuniary Personal non-pecuniary	Declare and participate
GC2 (3.9.13)	No change to existing declarations.	n/a	n/a
GC3 (8.10.13)	No change to existing declarations.	n/a	n/a
GC4 (19.11.13)	No change to existing declarations.	n/a	n/a
GC5&6 (27.1.14 & 28.1.14)	No change to existing declarations.	n/a	n/a
GC7 (3.3.14)	Research collaboration with MedImmune a biotech firm with links to AstraZeneca. No direct payments to Erol Gaillard or his research group. Member of the SIGN/BTS Asthma Guideline Development Group.	Personal non-pecuniary Personal non-pecuniary	Declare and participate
GC8 (8.4.14)	No change to existing declarations.	n/a	n/a
GC9 (13.5.14)	No change to existing declarations.	n/a	n/a
GC10 (16.6.14)	No change to existing declarations.	n/a	n/a
GC11 (22.7.14)	No change to existing declarations.	n/a	n/a
GC12 (2.9.14)	No change to existing declarations.	n/a	n/a
GC13 (7.10.14)	No change to existing declarations.	n/a	n/a
GC14 (30.3.15)	No change to existing declarations.	n/a	n/a
GC15 (9.5.17)	Received grants and consultancy paid to his institution from Vertex and Boehringer Ingelheim. Has research grants from Astra Zeneca and Circassia.	Specific non-personal pecuniary	Declare and withdraw for FeNO and the HE model but can answer questions on request by the Chair.
GC16 (15.8.17)	No change to existing declarations.	n/a	n/a

Catherine Lawlor

Date	Item declared	Classification	Action taken
GC1 (29.7.13)	Paid honoraria by Teva for position on "Integrated Care advisory board" May 2013. Paid honoraria by British Lung Foundation for development of "Train the Trainer COPD and Self Management" programme May / June 2013. PCRS-UK executive and PCRS-UK Nurse committee and receive Loss of Earnings payment plus travel expenses.	Non-specific personal pecuniary	Declare and participate
	Pending fee from British Lung Foundation for providing COPD training to GPs and Nurses in Hertfordshire. Honoraria received from TEVA for attending advisory meeting. Honoraria received from Almirall for attending nurse group meeting. Pending fee from RTA training for asthma update presentation for school nurses.	Non-specific personal pecuniary	Declare and participate
GC2 (3.9.13)	No change to existing declarations.	n/a	n/a
GC3 (8.10.13)	No change to existing declarations.	n/a	n/a
GC4 (19.11.13)	No change to existing declarations.	n/a	n/a
GC5&6 (27.1.14 & 28.1.14)	No change to existing declarations.	n/a	n/a
GC7 (3.3.14)	No change to existing declarations.	n/a	n/a
GC8 (8.4.14)	No change to existing declarations.	n/a	n/a
GC9 (13.5.14)	No change to existing declarations.	n/a	n/a
GC10 (16.6.14)	No change to existing declarations.	n/a	n/a
GC11 (22.7.14)	No change to existing declarations.	n/a	n/a
GC12 (2.9.14)	No change to existing declarations.	n/a	n/a
GC13 (7.10.14)	No change to existing declarations.	n/a	n/a

Date	Item declared	Classification	Action taken
GC14 (30.3.15)	No change to existing declarations.	n/a	n/a
GC15 (9.5.17)	Did not participate.	n/a	n/a
GC16 (15.8.17)	Did not participate.	n/a	n/a

Val Hudson

Date	Item declared	Classification	Action taken
GC1 (29.7.13)	None	n/a	n/a
GC2 (3.9.13)	Husband was commissioned by North Durham Clinical Commissioning Group (in shadow form) to carry out a piece of work on developing public and patient involvement in the CCG. This has now finished.	Personal family interest	Declare and participate
GC3 (8.10.13)	No change to existing declarations.	n/a	n/a
GC4 (19.11.13)	No change to existing declarations.	n/a	n/a
GC5&6 (27.1.14 & 28.1.14)	No change to existing declarations.	n/a	n/a
GC7 (3.3.14)	No change to existing declarations.	n/a	n/a
GC8 (8.4.14)	Attended a 1-hour Boehringer Ingelheim training event for their medical and marketing staff in Berlin. Received accommodation and travel expenses but no other reimbursements	Reasonable travel expenses	Declare and participate
GC9 (13.5.14)	No change to existing declarations.	n/a	n/a
GC10 (16.6.14)	No change to existing declarations.	n/a	n/a
GC11 (22.7.14)	No change to existing declarations.	n/a	n/a
GC12 (2.9.14)	No change to existing declarations.	n/a	n/a
GC13 (7.10.14)	No change to existing declarations.	n/a	n/a
GC14 (30.3.15)	No change to existing declarations.	n/a	n/a
GC15 (9.5.17)	No change to existing declarations.	n/a	n/a
GC16 (15.8.17)	No change to existing declarations.	n/a	n/a

Angela Key

Date	Item declared	Classification	Action taken
GC1 (29.7.13)	None	n/a	n/a
GC2 (3.9.13)	No change to existing declarations.	n/a	n/a
GC3 (8.10.13)	No change to existing declarations.	n/a	n/a
GC4 (19.11.13)	No change to existing declarations.	n/a	n/a
GC5&6 (27.1.14 & 28.1.14)	No change to existing declarations.	n/a	n/a
GC7 (3.3.14)	No change to existing declarations.	n/a	n/a
GC8 (8.4.14)	No change to existing declarations.	n/a	n/a
GC9 (13.5.14)	No change to existing declarations.	n/a	n/a
GC10 (16.6.14)	No change to existing declarations.	n/a	n/a
GC11 (22.7.14)	No change to existing declarations.	n/a	n/a
GC12 (2.9.14)	No change to existing declarations.	n/a	n/a
GC13 (7.10.14)	No change to existing declarations.	n/a	n/a
GC14 (30.3.15)	No change to existing declarations.	n/a	n/a
GC15 (9.5.17)	Did not participate.	n/a	n/a
GC16 (15.8.17)	Did not participate.	n/a	n/a

Matthew Masoli

Date	Item declared	Classification	Action taken
GC1 (29.7.13)	None	n/a	n/a
GC2 (3.9.13)	Received support from GSK to attend the EACCI conference in Milan (June 2013) and with Novartis for the ERS annual conference (Sept 2012). Support included registration and accommodation. In June 2013 received payment from GSK to do a talk on 'asthma control' as part of an allergy study day for GPs and practice nurses.	Non-specific personal pecuniary – (monitoring questionnaires review) ACT and CACT developed by GSK but both are freely available (non-profit making).	Declare and participate

Date	Item declared	Classification	Action taken
GC3 (8.10.13)	No change to existing declarations.	n/a	n/a
GC4 (19.11.13)	No change to existing declarations.	n/a	n/a
GC5&6 (27.1.14 & 28.1.14)	No change to existing declarations.	n/a	n/a
GC7 (3.3.14)	No change to existing declarations.	n/a	n/a
GC8 (8.4.14)	Speaker fee for an educational talk and workshop to healthcare professionals on 'reducing emergency asthma admissions' for a severe asthma study day sponsored by Novartis. March 2014.	Non-specific personal pecuniary	Declare and participate
GC9 (13.5.14)	Spoken presentation at a severe asthma symposium sponsored by Novartis in March 2014.	Non-specific personal pecuniary	Declare and participate
GC10 (16.6.14)	No change to existing declarations.	n/a	n/a
GC11 (22.7.14)	No change to existing declarations.	n/a	n/a
GC12 (2.9.14)	No change to existing declarations.	n/a	n/a
GC13 (7.10.14)	No change to existing declarations.	n/a	n/a
GC14 (30.3.15)	No change to existing declarations.	n/a	n/a
GC15 (9.5.17)	No change to existing declarations.	n/a	n/a
GC16 (15.8.17)	No change to existing declarations.	n/a	n/a

Melanie McFeeters

Date	Item declared	Classification	Action taken
GC1 (29.7.13)	Received speaker fees, expenses and hospitality from the pharmaceutical industry for both speaking and attending meetings in the past 12 months and which are planned but have not taken place yet. This includes fees for presenting educational talks to other healthcare professionals and hospitality for attending meetings and conferences related to the diagnosis and management of asthma. The companies include Abbott, Abbvie, AstraZeneca, GlaxoSmithKline, Novartis, Roche and Schering Plough.	Non-specific personal pecuniary – (monitoring questionnaires review) ACT and CACT developed by GSK but both are freely available (non-profit making).	Declare and participate

Date	Item declared	Classification	Action taken
	Member of the British Thoracic Society (BTS) and committee member of the BTS Nurse Advisory Group. Member of the BTS/SIGN 101 British Guideline on the Management of Asthma Guideline Development Group – Organisation and Delivery of Care. RCN Member.	Personal non-pecuniary	
GC2 (3.9.13)	No change to existing declarations.	n/a	n/a
GC3 (8.10.13)	No change to existing declarations.	n/a	n/a
GC4 (19.11.13)	No change to existing declarations.	n/a	n/a
GC5&6 (27.1.14 & 28.1.14)	No change to existing declarations.	n/a	n/a
GC7 (3.3.14)	Speaker fee received for educational talk to Healthcare Professionals (GP & PNs) on 30/1/14. Meeting sponsored by GSK. Talk presented - Asthma management in children. Steering committee/Advisory board meeting attended on 3/2/14 for AbbVie in preparation for the EMBRACE 2014 meeting – Prophylaxis for RSV.	Non-specific personal pecuniary	Declare and participate
GC8 (8.4.14)	No change to existing declarations.	n/a	n/a
GC9 (13.5.14)	No change to existing declarations.	n/a	n/a
GC10 (16.6.14)	No change to existing declarations.	n/a	n/a
GC11 (22.7.14)	No change to existing declarations.	n/a	n/a
GC12 (2.9.14)	No change to existing declarations.	n/a	n/a
GC13 (7.10.14)	No change to existing declarations.	n/a	n/a
GC14 (30.3.15)	No change to existing declarations.	n/a	n/a
GC15 (9.5.17)	No change to existing declarations.	n/a	n/a
GC16 (15.8.17)	No change to existing declarations.	n/a	n/a

Tahmina Siddiqui

Date	Item declared	Classification	Action taken

Date	Item declared	Classification	Action taken
GC1 (29.7.13)	None	n/a	n/a
GC2 (3.9.13)	Member of iCOPD template development group in conjunction with PCRS UK, funded by Kendle Healthcare. Attended ERS in September 2102, also to attend a iCOPD meeting funded by Kendle Healthcare. Lead GP for COPD in Milton Keynes. Long term intervention team (LIT) chairperson Milton Keynes.	Non-specific personal non-pecuniary Non-specific personal pecuniary Non-specific personal non-pecuniary	Declare and participate
GC3 (8.10.13)	No change to existing declarations.	n/a	n/a
GC4 (19.11.13)	Chaired a GP study day COPD Master class on September 2013 sponsored by Almirral. Attended 1st COPD world Summit conference in Lisbon Sponsored by Almirral.	Non-specific personal pecuniary	Declare and participate
GC5&6 (27.1.14 & 28.1.14)	No change to existing declarations.	n/a	n/a
GC7 (3.3.14)	No change to existing declarations.	n/a	n/a
GC8 (8.4.14)	No change to existing declarations.	n/a	n/a
GC9 (13.5.14)	No change to existing declarations.	n/a	n/a
GC10 (16.6.14)	No change to existing declarations.	n/a	n/a
GC11 (22.7.14)	No change to existing declarations.	n/a	n/a
GC12 (2.9.14)	No change to existing declarations.	n/a	n/a
GC13 (7.10.14)	No change to existing declarations.	n/a	n/a
GC14 (30.3.15)	No change to existing declarations.	n/a	n/a
GC15 (9.5.17)	No change to existing declarations.	n/a	n/a
GC16 (15.8.17)	No change to existing declarations.	n/a	n/a

Mike Thomas

Date	Item declared	Classification	Action taken
GC1 (29.7.13)	Received honoraria for attending advisory panels from the following companies manufacturing respiratory products in the past 12 months: GlaxoSmithKline Almirall Novartis. Received sponsorship to attend the European Respiratory Society meeting from Napp (standard travel and hotel). Holds a research study funded by GSK.	Non-specific personal pecuniary – (monitoring questionnaires review) ACT and CACT developed by GSK but both are freely available (non-profit making). Non-specific non-personal pecuniary	Declare and participate
	Received an honorarium for speaking at the ERS at the Aerocrine sponsored symposium.	Specific personal pecuniary	Declare and withdraw for FeNO
	Received speaker's honoraria for speaking at sponsored meetings from the following companies marketing respiratory and allergy products: Aerocrine, Astra Zeneca, Boehringer Inglehiem, GSK, MSD, Napp, Schering-Plough, Teva. Received honoraria for attending advisory panels with; Aerocrine, Almirall, Astra Zeneca, BI, Chiesi, GSK, MSD, Merck Respiratory, Schering-Plough, Teva, Novartis. Received sponsorship to attend international scientific meetings from: GSK, MSD, Astra Zeneca, Mundipharma. Received funding for research projects from: GSK, Almirall. Michael Thomas is chief medical adviser to the charity Asthma UK, a member of the BTS SIGN Asthma guideline group and a member of the EPOS Rhinosinusitis guideline group.	Specific personal pecuniary Non-specific non-personal pecuniary Personal non-pecuniary	Declare and withdraw for FeNO

Date	Item declared	Classification	Action taken
	Spoke at the ERS on the use of exhaled nitric oxide in the diagnosis and management of asthma and spoke to the NICE team on this topic as an expert witness.		
	Department has received an honorarium for Michael Thomas speaking at the ERS at the Aerocrine sponsored symposium; department also received honoraria for Michael Thomas to attend an advisory board and for giving a talk at a GP educational meeting. Department received honoraria for producing a research study protocol for Novartis.	Specific non-personal pecuniary interest Non-specific non-personal pecuniary	Declare and withdraw for FeNO and the HE model but can answer questions on request by the Chair.
GC2 (3.9.13)	No change to existing declarations.	n/a	n/a
GC3 (8.10.13)	No change to existing declarations.	n/a	n/a
GC4 (19.11.13)	No change to existing declarations.	n/a	n/a
GC5&6 (27.1.14 & 28.1.14)	No change to existing declarations.	n/a	n/a
GC7 (3.3.14)	No change to existing declarations.	n/a	n/a
GC8 (8.4.14)	No change to existing declarations.	n/a	n/a
GC9 (13.5.14)	No change to existing declarations.	n/a	n/a
GC10 (16.6.14)	No change to existing declarations.	n/a	n/a
GC11 (22.7.14)	Department received an honorarium from Aerocrine (makers of a FENO monitor) for Michael Thomas's attendance at an advisory meeting to discuss research needs in the FENO evidence, and there is discussion of a possible Horizon 2020 grant application for a multinational collaborative EU-Industry funded project. Department received funding from GSK as Michael Thomas is the Chief Investigator and chair of the steering committee of an international study investigating inhaler device errors. Received an honorarium from Boehringer Ingelheim for attendance at a meeting	Specific non-personal pecuniary interest Non-specific non-personal pecuniary Non-specific personal pecuniary	Declare and withdraw for FeNO and the HE model but can answer questions on request by the Chair.

Date	Item declared	Classification	Action taken
	organising a collaborative project with the University of Nottingham/PRIMIS to create an asthma electronic audit tool for use in general practice, and from Novartis for speaking at meeting on COPD.		
GC12 (2.9.14)	No change to existing declarations.	n/a	n/a
GC13 (7.10.14)	No change to existing declarations.	n/a	n/a
GC14 (30.3.15)	No change to existing declarations.	n/a	n/a
GC15 (9.5.17)	No change to existing declarations and previously declared conflict of interest with Aerocrine now expired.	n/a	Declare and participate
GC16 (15.8.17)	No change to existing declarations.	n/a	n/a

NGC team

Date	Item declared	Classification	Action taken
GC1 (29.7.13)	In receipt of NICE commissions. Bernard Higgins is Chair of the British Thoracic Society.	n/a Non-specific personal non-pecuniary	n/a Declare and participate
GC2 (3.9.13)	No change to existing declarations.	n/a	n/a
GC3 (8.10.13)	No change to existing declarations.	n/a	n/a
GC4 (19.11.13)	No change to existing declarations.	n/a	n/a
GC5&6 (27.1.14 & 28.1.14)	No change to existing declarations.	n/a	n/a
GC7 (3.3.14)	No change to existing declarations.	n/a	n/a
GC8 (8.4.14)	No change to existing declarations.	n/a	n/a
GC9 (13.5.14)	No change to existing declarations.	n/a	n/a
GC10 (16.6.14)	No change to existing declarations.	n/a	n/a
GC11 (22.7.14)	No change to existing declarations.	n/a	n/a
GC12 (2.9.14)	No change to existing declarations.	n/a	n/a

Date	Item declared	Classification	Action taken
GC13 (7.10.14)	No change to existing declarations.	n/a	n/a
GC14 (30.3.15)	No change to existing declarations.	n/a	n/a
GC15 (9.5.17)	No change to existing declarations.	n/a	n/a
GC16 (15.8.17)	No change to existing declarations.	n/a	n/a

Cochrane team

Date	Item declared	Classification	Action taken
Initial declaration (Dec 13)	None	n/a	n/a
GC10 (16.6.14)	No change to existing declarations.	n/a	n/a

NIHR team

Date	Item declared	Classification	Action taken
Initial declaration (May 14)	None	n/a	n/a
GC12 (2.9.14)	No change to existing declarations.	n/a	n/a

Appendix C: Review protocols

C.1 Diagnosis: Signs and symptoms

Table 1: Review protocol: Signs and symptoms for asthma diagnosis

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic accuracy of each of the following signs and symptoms? • wheezing • cough • breathlessness • nocturnal symptoms • diurnal and seasonal variations
Objectives	To evaluate the diagnostic accuracy of signs and symptoms in diagnosing asthma
Study design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses)
Population / Target condition	People with suspected asthma (presenting with respiratory symptoms). All ages, stratified into the following 3 different groups: • Children (1-<5 years old) • Children/young people (5-16 years old) • Adults (>16 years old)
Setting	Primary, secondary and community care settings
Index test	Signs and symptoms of asthma Each of the following symptoms alone or in combination: • Wheezing (current or persistent or triggered) • Cough (including nocturnal cough) • Breathlessness • Nocturnal symptoms • Diurnal and seasonal variations
Reference standard	Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold. Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis.

	In children 1-<5 years, objective tests cannot be performed so the reference standard will be physician diagnosis based on recurrent and persistent wheezing.
Outcomes	• Diagnostic accuracy (sensitivity and specificity)
Other exclusions	• Not looking at occupational asthma /allergens • Not looking at factors which influence signs/symptoms • Due to anticipation of there being a large amount of studies retrieved from the search, the inclusion criteria was limited to studies which only look at populations in the UK, USA, Australia, Canada, New Zealand and Western Europe*. These countries were expected to be similar to the UK in terms of how people report symptoms and the impact of language. If relevant studies were identified from other review questions reporting populations outside these countries then these were included. *Western Europe = Austria, Belgium, France, Germany, Liechtenstein, Luxembourg, Monaco, Netherlands, Switzerland
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using the QUADAS-II checklist. Synthesis of data • Diagnostic meta-analysis will be conducted where appropriate. If no/insufficient evidence is found we will (in order of preference): • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Move to GC consensus
Analysis-subgroups to investigate heterogeneity	• Different test thresholds • Different reference standards • Combinations of symptoms

C.2 Diagnosis: History of atopic disorders

Table 2: Review protocol: History of atopic disorders for asthma diagnosis

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic accuracy of taking a personal/family history of atopic disorders?
Objectives	To evaluate the diagnostic test value of taking a personal/family history of atopic disorders in diagnosing asthma
Study design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses)
Population / Target condition	People with suspected asthma (presenting with respiratory symptoms). All ages, stratified into the following 3 different groups: • Children (1-<5 years old) • Children/young people (5-16 years old) • Adults (>16 years old)
Setting	Primary, secondary and community care settings

Index test	Personal/family history of atopic disorders. • This is likely to be ascertained by a questionnaire. NOTE: personal history is defined as an individual who has had one of the atopic disorders listed below NOTE: family history is defined as: 1st degree relatives. NOTE: atopic disorders are defined as: eczema, hay fever, allergic rhinitis, food allergy, asthma.
Reference standard	Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold. Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis. In children 1-<5 years, objective tests cannot be performed so the reference standard will be physician diagnosis based on recurrent and persistent wheezing.
Outcomes	• Diagnostic accuracy (sensitivity and specificity)
Other exclusions	• Not looking at occupational asthma /allergens • Not looking at other factors which influence this
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using the QUADAS-II checklist. Synthesis of data • Diagnostic meta-analysis will be conducted where appropriate. If no/insufficient evidence is found we will (in order of preference): • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Move to GC consensus
Analysis-subgroups to investigate heterogeneity	• Different reference standards

C.3 Diagnosis: Symptoms after exercise

Table 3: Review protocol: Symptoms after exercise for asthma diagnosis

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic accuracy of a clinical history of symptoms in response to exercise?
Objectives	To evaluate the diagnostic test value of taking a clinical history of symptoms in response to exercise in diagnosing asthma
Study design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses)
Population / Target condition	People with suspected asthma (presenting with respiratory symptoms). All ages, stratified into the following 3 different groups: • Children (1- <5 years old) • Children/young people (5-16 years old) • Adults (>16 years old)
Setting	Primary, secondary and community care settings
Index test	Clinical history of symptoms in response to exercise. NOTE: symptoms would be a combination of the following, or individual symptoms – wheezing, cough, breathlessness
Reference standard	Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold. Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis. In children 1-<5 years, objective tests cannot be performed so the reference standard will be physician diagnosis based on recurrent and persistent wheezing.
Statistical measures	Diagnostic accuracy (sensitivity, specificity)
Other exclusions	• Not occupational asthma /allergens • Not looking at other factors which influence signs/symptoms (this includes seasonal variation) • Not looking at tests in athletes or professional / specialist sports • Not looking at validation studies, or studies comparing different methods of measuring clinical history of symptoms after exercise.

	Not looking at 'case-control' type studies where the index test is applied in people with confirmed asthma and healthy controls, and where there is no uncertainty about whether the patient has asthma or not. Such studies only include a spectrum of the disease and non-diseased patients and the diagnostic test accuracy may not be applicable to the clinical question.
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using the QUADAS-II checklist. Synthesis of data • Diagnostic meta-analysis will be conducted where appropriate. If no/insufficient evidence is found we will (in order of preference): • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Move to GC consensus
Analysis- subgroups to investigate heterogeneity	None

C.4 Diagnosis: Symptoms after using medication

Table 4: Review protocol: Symptoms after using medication for asthma diagnosis

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic accuracy of a clinical history of symptoms after taking the following drugs: a) in adults - beta blockers, aspirin, or other NSAIDs b) in children – ibuprofen?
Objectives	To evaluate the diagnostic test value of taking a clinical history of worsening asthma symptoms after taking drugs (aspirin or other NSAIDs and beta blockers)?
Study Design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses)
Population/ Target condition	People with suspected asthma (presenting with respiratory symptoms). All ages, stratified into the following 3 different groups: • Children (1-<5 years old) - for ibuprofen only • Children/young people (5-16 years old) – for ibuprofen only • Adults (>16 years old) – for beta blockers, aspirin or other NSAIDs
Setting	Primary, secondary and community care settings
Index test	Clinical history of symptoms after taking drugs. NOTE: drugs of interest for the adult population are aspirin and NSAIDs, beta blockers. For children – ibuprofen. NOTE: symptoms would be a combination of the following, or individual symptoms – wheezing, cough, breathlessness, nocturnal symptoms, diurnal and seasonal variations.
Reference standard	Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test);

Component	Description
	• bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold. Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis.
Outcomes	Diagnostic accuracy (sensitivity, specificity)
Other exclusions	Not occupational asthma /allergens Not looking at other factors which influence signs/symptoms
Search strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using the QUADAS-II checklist. Synthesis of data • Diagnostic meta-analysis will be conducted where appropriate. If no/insufficient evidence is found we will (in order of preference): • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Move to GC consensus
Analysis-subgroups to investigate heterogeneity	None

C.5 Diagnosis: Occupational asthma

Table 5: Review protocol: Occupational asthma diagnosis

Component	Description
Review question	In adults under investigation for occupational asthma, what is the diagnostic accuracy for case identification, of asking whether their symptoms are better away from work?
Objectives	To evaluate the diagnostic test value (for identifying occupational asthma), of asking whether symptoms are better away from work?
Study design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses)
Population / Target condition	Adults (>16 years old) with suspected occupational asthma.
Setting	Primary, secondary and community care settings
Index test	Symptoms are better away from work. NOTE: symptoms are defined as – wheezing, cough, breathlessness, nocturnal symptoms, diurnal variations
Reference standard	Physician's diagnosis of occupational asthma supported by an objective test (e.g. specific inhalation challenge)

Outcomes	Diagnostic accuracy (sensitivity, specificity)
Other exclusions	
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using the QUADAS-II checklist. Synthesis of data • Diagnostic meta-analysis will be conducted where appropriate. If no/insufficient evidence is found we will (in order of preference): • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Move to GC consensus
Analysis-subgroups to investigate heterogeneity	Occupational differences (different causal agents)

C.6 Diagnosis: Spirometry

Table 6: Review protocol: Spirometry for asthma diagnosis

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of spirometry / flow volume loop measures?
Objectives	To evaluate the diagnostic test value of spirometry / flow volume loop measures in diagnosing asthma
Study design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses)
Population / Target condition	People with suspected asthma (presenting with respiratory symptoms). Ages stratified into the following 2 groups: • Children/young people (5-16 years old) • Adults (>16 years old)
Setting	Primary, secondary and community care settings
Index test	Spirometry measures (report separately) • FEV1/FVC ratio (<70%) • Flow volume loop (graph) • FEV1 (<80%) – if limited evidence from the above two measures Pre bronchodilator values (applies for all above measures) FEV1 and FVC should be performed using the following criteria: • Forced expiratory volume (FEV1) - patients perform manoeuvre until 3 readings are within 5% of each other (maximum 8 attempts) the measured value being the best of these 3 readings. • Forced vital capacity (FVC) - patients perform manoeuvre until 3 readings are within 5% of each other (maximum 8 attempts) the measured value being the best of these 3 readings.
Reference standard	Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold. Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis.
Outcomes	• Diagnostic accuracy (sensitivity and specificity)

Other exclusions	• Not looking at occupational asthma /allergens • Not looking at validation studies, or studies comparing different spirometry or flow volume loop measures • Not looking at factors which influence measurements
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using the QUADAS-II checklist. Synthesis of data • Diagnostic meta-analysis will be conducted where appropriate. If no/insufficient evidence is found we will (in order of preference): • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Move to GC consensus
Analysis-subgroups to investigate heterogeneity	• Different reference standards

C.7 Diagnosis: Bronchodilator reversibility

Table 7: Review protocol: Bronchodilator reversibility for asthma diagnosis

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of bronchodilator response (using PEF or FEV1)?
Objectives	To evaluate the diagnostic test value of bronchodilator response (using PEF or FEV1) in diagnosing asthma
Study design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses)
Population / Target condition	People with suspected asthma (presenting with respiratory symptoms). Ages stratified into the following 2 groups: • Children/young people (5-16 years old) • Adults (>16 years old)
Setting	Primary, secondary and community care settings
Index test	Bronchodilator response, measured using the following • PEF • FEV1 ○ change in FEV1 % initial and change in FEV1 litres Exclusions: • Change in FEV1 % initial alone Change in absolute litres alone • Change in FEV1 % predicted (ΔFEV1 %pred) • Standardised residual (SR)-FEV1 • Change in FEV1 % of possible maximal response (ΔFEV1 %max)
Reference standard	Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold. Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis.
Outcomes	• Diagnostic accuracy (sensitivity and specificity)
Other exclusions	• Not occupational asthma /allergens • Not looking at validation studies, or studies comparing different methods of measuring the same test

	• Not looking at factors which influence measurements
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using the QUADAS-II checklist. Synthesis of data • Diagnostic meta-analysis will be conducted where appropriate. If no/insufficient evidence is found we will (in order of preference): • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Move to GC consensus
Analysis-subgroups to investigate heterogeneity	• Different test thresholds • Different reference standards

C.8 Diagnosis: PEF variability

Table 8: Review protocol: Peak expiratory flow (PEF) variability for asthma diagnosis

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of peak expiratory flow (PEF) variability?
Objectives	To evaluate the diagnostic test value of PEF variability in diagnosing asthma
Study design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses)
Population / Target condition	People with suspected asthma (presenting with respiratory symptoms). All ages, stratified into the following 2 different groups: • Children/young people (5-16 years old) • Adults (>16 years old)
Setting	Primary, secondary and community care settings
Index test	PEF variability (diurnal variability usually expressed as amplitude (highest – lowest reading) as a percentage of the mean or the highest reading). PEFv values should be recorded as the mean over a period of at least 3 days)
Reference standard	Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an

	objective test using an alternative threshold. Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis.
Outcomes	• Diagnostic accuracy (sensitivity, specificity)
Other exclusions	• Not occupational asthma /allergens • Not looking at validation studies, or studies comparing different PEF measures • Not looking at factors which influence measurements
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using the QUADAS-II checklist. Synthesis of data • Diagnostic meta-analysis will be conducted where appropriate. If no/insufficient evidence is found we will (in order of preference): • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Move to GC consensus
Analysis-subgroups to investigate heterogeneity	• Different test thresholds • Different reference standards

C.9 Diagnosis: Skin prick tests

Table 9: Review protocol: Skin prick tests for asthma diagnosis

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of skin prick tests?
Objectives	To evaluate the diagnostic test value of skin prick tests in diagnosing asthma
Study design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses)
Population / Target condition	People with suspected asthma (presenting with respiratory symptoms). All ages, stratified into the following 3 different groups: • Children (1-<5 years old) • Children/young people (5-16 years old) • Adults (>16 years old)
Setting	Primary, secondary and community care settings
Index test	Skin prick tests for the most common allergens (reported separately) • House dust mites • Cat • Dog • Grass pollen* (native UK grasses) • Tree pollen* (native UK trees)

	• Mixed pollens* (native UK species) • *Aspergillus* • *Alternaria* • *Cladosporium* Cut off values: 3mm WHEAL (skin reaction) greater than the negative control in the presence of a positive control * Mainland Europe (including Denmark; excluding Norway, Sweden, Finland, Iceland, Russia, Greece), North America (USA + Canada), Australia, New Zealand (as trees/grasses/pollen similar to UK in included countries but not in other countries)
Reference standard	Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold. Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis. In children 1-<5 years, objective tests cannot be performed so the reference standard will be physician diagnosis based on recurrent and persistent wheezing.
Outcomes	• Diagnostic accuracy (Sensitivity and specificity)
Other exclusions	• Not occupational asthma /allergens • Not looking at validation studies, or studies comparing different skin prick methods • Not looking at factors which influence skin prick measurements • Studies in which we are unable to calculate sensitivity and specificity (unless sensitivity/specificity has been reported by the study).
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Search terms	
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using the QUADAS-II checklist. Synthesis of data • Diagnostic meta-analysis will be conducted where appropriate. If no/insufficient evidence is found we will (in order of preference): • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information)

	• Move to GC consensus
Analysis-subgroups to investigate heterogeneity	• Different test thresholds • Different reference standards • Age groups • People with eczema • Personal or family history of atopy

C.10 Diagnosis: IgE

Table 10: Review protocol: Serum IgE for asthma diagnosis

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of total and specific serum IgE measures?
Objectives	To evaluate the diagnostic test value of serum IgE in diagnosing asthma
Study design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses)
Population / Target condition	People with suspected asthma (presenting with respiratory symptoms). All ages, stratified into the following 3 different groups: • Children (1-<5 years old) • Children/young people (5-16 years old) • Adults (>16 years old)
Setting	Primary, secondary and community care settings
Index test	Serum IgE • Total IgE • Specific IgE* (including RAST test) *Reported separately t for the most common aero-allergens (dust mites, grass pollen, tree pollen, dog, cat, *Aspergillus, Alternaria, Cladosporium*). NOTE: serum IgE must have been assessed using ELISA (apart from RAST) as other techniques are not current/no longer used.
Reference standard	Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold. Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis.

	In children 1-<5 years, objective tests cannot be performed so the reference standard will be physician diagnosis based on recurrent and persistent wheezing.
Outcomes	• Diagnostic accuracy (Sensitivity and specificity)
Other exclusions	• POPULATION: o Occupational asthma /allergens o Mixed populations of asthma with other groups such as rhinitis (unless the results for the subgroup of asthma patients have been reported separately). • TESTS: o Validation studies, or studies comparing different methods of measuring IgE. o Studies that do not use ELISA for determining presence of IgE. • ANALYSIS/RESULTS: o Studies that look at levels of IgE o Studies that assess factors that may influence IgE measurements (eg. smoking, age, gender) o Studies that use IgE predict the development of asthma at a later follow-up time o Studies that look at correlations or agreement between tests, but not numbers of patients who were positive and negative o Studies that look at IgE to in relation to asthma severity • STUDY TYPES: o Case-control studies will be excluded if there are few 'true' diagnostic studies
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using the QUADAS-II checklist. Synthesis of data • Diagnostic meta-analysis will be conducted where appropriate. If no/insufficient evidence is found we will (in order of preference): • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Move to GC consensus
Analysis-subgroups to investigate heterogeneity	• Different test thresholds • Different reference standards

C.11 Diagnosis: FeNO

Table 11: Review protocol: FeNO for asthma diagnosis

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of fractional exhaled nitric oxide (FeNO) measures?
Objectives	To evaluate the diagnostic test value of FeNO in diagnosing asthma
Study design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses) Case-control studies were included for the comparison of FeNO levels only
Population / Target condition	People with suspected asthma (presenting with respiratory symptoms). All ages, stratified into the following 3 different groups: • Children (1-<5 years old) • Children/young people (5-16 years old) • Adults (>16 years old)
Setting	Primary, secondary and community care settings
Index test	Fractional exhaled nitric oxide (FeNO) with a cut-off threshold between 20-50ppb and a flow rate of 50ml/s or equivalent
Reference standard	Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold. Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis. In children 1-<5 years, objective tests cannot be performed so the reference standard will be physician diagnosis based on recurrent and persistent wheezing.
Outcomes	• Diagnostic accuracy (Sensitivity and specificity) • FeNO levels
Other exclusions	• Studies in which >50% of people are on corticosteroid treatment • Not looking at occupational asthma /allergens • Not looking at validation studies, or studies comparing different methods of measuring FeNO. • Cross-sectional studies were included if they reported sensitivity or specificity, or the sensitivity and specificity could be calculated. • Case-control studies were only included if they reported levels of FeNO, but they had to have a sample size of N>50.

Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using the QUADAS-II checklist. Synthesis of data • Diagnostic meta-analysis will be conducted where appropriate. If no/insufficient evidence is found we will (in order of preference): • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Move to GC consensus
Analysis-subgroups to investigate heterogeneity	Are there any subgroups to consider? • Different test thresholds • Sequence step of the test (eg, first test, second test etc) • Commercially available meters

C.12 Diagnosis: Peripheral blood eosinophils

Table 12: Review protocol: Peripheral blood eosinophil count for asthma diagnosis

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of eosinophil blood count measures?
Objectives	To evaluate the diagnostic test value of eosinophil blood count in diagnosing asthma
Study design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses) Case-control studies were included for the comparison of blood eosinophil levels only
Population / Target condition	People with suspected asthma (presenting with respiratory symptoms). All ages, stratified into the following 3 different groups: • Children (1- <5 years old) • Children/young people (5-16 years old) • Adults (>16 years old)
Setting	Primary, secondary and community care settings
Index test	Peripheral blood eosinophil count (may be part of FBC)
Reference standard	Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold.

	Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis. In children 1-<5 years, objective tests cannot be performed so the reference standard will be physician diagnosis based on recurrent and persistent wheezing.
Outcomes	• Diagnostic accuracy (sensitivity, specificity) • Eosinophil levels
Other exclusions	• Not looking at occupational asthma /allergens • Not looking at validation studies, or studies comparing different methods of measuring eosinophil blood counts. • Not looking at factors which influence eosinophil measurements • Cross-sectional studies were included if they reported sensitivity or specificity, or the sensitivity and specificity could be calculated. If they reported levels of blood eosinophils, then they were excluded. • Case-control studies were only included if they reported levels of blood eosinophils, but they had to have a sample size of N>50.
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using the QUADAS-II checklist. Synthesis of data • Diagnostic meta-analysis will be conducted where appropriate. If no/insufficient evidence is found we will (in order of preference): • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Move to GC consensus
Analysis-subgroups to investigate heterogeneity	• Different test thresholds • Different reference standards • Sequence step of the test (eg, first test, second test etc) • Eosinophil counts: >1, 0.4-0.9, 0.2-0.4

C.13 Diagnosis: Histamine and methacholine

Table 13: Review protocol: Histamine and methacholine challenge tests for asthma diagnosis

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of airway hyper-reactivity (non-specific bronchial challenge) with histamine and methacholine?
Objectives	To evaluate the diagnostic test value of histamine and methacholine PC20 in diagnosing asthma
Study design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses)
Population / Target condition	People with suspected asthma (presenting with respiratory symptoms). Ages stratified into the following 2 different groups: • Children/young people (5-16 years old) • Adults (>16 years old)
Setting	Primary, secondary and community care settings
Index test	• Histamine PC20 and PD20 • Methacholine PC20 and PD20 Cut-off threshold of 8mg/ml or a cut-off threshold identified from a ROC curve
Reference standard	Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test). Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold. Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis.
Statistical measures	• Diagnostic accuracy (sensitivity and specificity)
Other exclusions	• Not occupational asthma /allergens • Not looking at validation studies, or studies comparing different methods of measuring the same test • Not looking at factors which influence measurements • Not looking at 'case-control' type studies where the index test is applied in people with confirmed asthma and healthy controls, and where there is no uncertainty about whether the patient has asthma or not. Such studies only include a spectrum of the disease and non-diseased patients and the diagnostic test accuracy may not be applicable to the clinical question.
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using the QUADAS-II

	checklist. Synthesis of data • Diagnostic meta-analysis will be conducted where appropriate. If no/insufficient evidence is found we will (in order of preference): • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Move to GC consensus

C.14 Diagnosis: Mannitol

Table 14: Review protocol: Mannitol challenge test for asthma diagnosis

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness ofairway hyper-reactivity (non-specific bronchial challenge) with mannitol?
Objectives	To evaluate the diagnostic test value ofmannitol in diagnosing asthma
Study design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses)
Population / Target condition	People with suspected asthma (presenting with respiratory symptoms). Ages stratified into the following 2 different groups: • Children/young people (5-16 years old) • Adults (>16 years old)
Setting	Primary, secondary and community care settings
Index test	• Mannitol
Reference standard	Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold. Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis.
Statistical measures	Diagnostic accuracy (sensitivity, specificity)
Other exclusions	• Not occupational asthma /allergens • Not looking at validation studies, or studies comparing different methods of measuring the same test • Not looking at factors which influence measurements

Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using the QUADAS-II checklist. Synthesis of data • Analyse mannitol challenge methods and kits separately (split) • Diagnostic meta-analysis will be conducted where appropriate. If no/insufficient evidence is found we will (in order of preference): • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Move to GC consensus
Analysis-subgroups to investigate heterogeneity	• Different test thresholds • Different reference standards

C.15 Diagnosis: Exercise challenge test

Table 15: Review protocol: Exercise challenge test for asthma diagnosis

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic accuracy of bronchoconstriction in response to an exercise challenge?
Objectives	To evaluate the diagnostic test value of bronchoconstriction in response to an exercise challenge, in diagnosing asthma
Study design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses)
Population / Target condition	People with suspected asthma (presenting with respiratory symptoms). Ages stratified into the following 2 different groups: • Children/young people (5-16 years old) • Adults (>16 years old)
Setting	Primary, secondary and community care settings
Index test	Exercise challenge test (>10% FEV1 bronchoconstriction in response to exercise – within 15 mins) 1. Change in FEV1 ≥10% post-exercise 2. If the study has used a cut-off based on performing a ROC NOTE: usually this is a 6 minute exercise challenge test.
Reference standard	Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test)

	Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold. Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis.
Outcomes	• Diagnostic accuracy (sensitivity and specificity)
Other exclusions	• Not occupational asthma /allergens • Not looking at tests in athletes • Not looking at other factors which influence signs/symptoms
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	Appraisal of methodological quality • The methodological quality of each study will be assessed using the QUADAS-II checklist. Synthesis of data • Diagnostic meta-analysis will be conducted where appropriate. If no/insufficient evidence is found we will (in order of preference): • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Move to GC consensus
Analysis-subgroups to investigate heterogeneity	• Different test thresholds • Different reference standards

C.16 Monitoring: Questionnaires

Table 16: Review protocol: Symptom scores/diaries or validated questionnaires to monitor asthma control

Component	Description
Review question	In people with asthma, what is the clinical and cost-effectiveness of using symptom scores / diaries or validated questionnaires measuring symptom control (eg ACT, ACQ, CACT, RCP 3 questions) and/or health related quality of life (eg AQLQ, PAQLQ) to monitor asthma?
Objectives	To evaluate the clinical and cost-effectiveness of using symptom scores / diaries or validated questionnaires that measure symptoms or HRQoL to monitor asthma? Questionnaires that measure current disease impact and future risk of exacerbation; does measuring symptom control and QoL in asthma patients, improve patient outcomes?
Study design	• RCTs • Validation studies (in different age groups) – summarise these narratively.
Population / Target condition	People with asthma (defined as physician Dx with objective test or recurrent persistent wheeze in <5 years). If insufficient evidence is found we will consider evidence from studies where asthma is defined as physician Dx only or on asthma treatment (give details of how Dx was made). Not including severe asthma. All ages, stratified into the following 3 different groups: • Children (1-<5 years old)

	• Children/young people (5-16 years old) • Adults (>16 years old)

Intervention	Monitoring the following, and using the outcomes of scores/questionnaires to adjust management/therapy according to physician decision or personalised treatment plan (use of other interventions to be included if equal access in each group, eg both groups receive education in addition to monitoring):
	
	• Symptom scores or diaries
	• Symptom/control questionnaires
	  ○ Asthma Control Test, ACT (including caregivers or paediatric version, CACT)
	  ○ Asthma Control Questionnaire, ACQ (including mini ACQ or paediatric ACQ)
	  ○ RCP 3 questions
	• Quality of life questionnaires (asthma specific)
	  ○ HS QoL
	  ○ Asthma Quality of Life Questionnaire, AQLQ (including paeds version, PAQLQ)

Comparison	Comparison of adjustment of asthma therapy based on symptom scores or questionnaires to: • Usual care: eg clinical symptoms (with/without spirometry/PEF) according to guidelines (including BTS/SIGN, GINA) Comparison of adjustment of asthma therapy based on: • Symptom scores or diaries vs questionnaires • Control questionnaire vs other control questionnaire • QOL questionnaire vs control questionnaire
Outcomes	Critical outcomes: • Mortality • Unscheduled healthcare utilisation (ED/A&E visit; hospital admissions; GP out of hours or walk-in centre) • Exacerbations (defined as need for course of oral steroids) • Asthma control questionnaires (ACT; CACT; ACQ; PACQ; RCP-3) • QoL (AQLQ; pAQLQ; St George's respiratory questionnaire) Important outcomes: • Lung function (FEV1, PEF) • Symptoms (annual symptom free days) • Dose of regular asthma therapy / preventer medication (ICS dose) • Rescue medication (SABA use) • Time off school or work
Exclusions	• Exclude observational cohort studies and NRS unless limited evidence from RCTs • Studies not in English • Not occupational asthma /allergens
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	Stratify by age group Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Synthesis of data • Meta-analysis will be conducted where appropriate • Outcomes will be grouped into the following categories based on time-points:

	○ <6 months (or the one nearest to 6 months if multiple time-points are given) ○ ≥6 months (or the longest one if multiple time-points are given) Default MIDs will be used where no MIDs are established: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes If no/insufficient evidence is found we will (in order of preference): • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Consider observational studies and NRS • Consider prognostic studies • Move to GC consensus
Analysis-subgroups to investigate heterogeneity	• Ethnic groups (e.g. south Asians, African Americans, Hispanics) • Education levels • Language (non English speaking)

C.17 Monitoring: Lung function tests

Table 17: Review protocol: Lung function tests to monitor asthma control

Component	Description
Review question	In people with asthma, what is the clinical and cost-effectiveness of using measures of pulmonary function assessing asthma control (for example, spirometry and peak expiratory flow) to monitor asthma?
Objectives	To evaluate the clinical and cost-effectiveness of using measures of pulmonary function assessing asthma control (for example, spirometry and peak expiratory flow) to monitor asthma.
Study design	• RCTs
Population / Target condition	People with asthma (defined as physician Dx with objective test). If insufficient evidence is found we will consider evidence from studies where asthma is defined as physician Dx only or on asthma treatment (give details of how Dx was made). Not including severe asthma. All ages, stratified into the following 2 different groups: • Children/young people (5-16 years old) • Adults (>16 years old)
Intervention	Monitoring lung function using the following tests, and using the outcomes to adjust management/therapy according to physician decision or personalised treatment plan (use of other interventions to be included if equal access in each group, eg both groups receive education in addition to monitoring): • Spirometry (FEV1; FEV1/FVC; Flow loop measures) • PEF
Comparison	Comparison of adjustment of asthma therapy based on lung function tests to: • Usual care: eg clinical symptoms according to guidelines (including BTS/SIGN, GINA) • Asthma control or QOL questionnaires Comparison of adjustment of asthma therapy based on: • Spirometry versus PEF
Outcomes	Critical outcomes: • Mortality • Unscheduled healthcare utilisation (ED/A&E visit; hospital admissions; GP out of

	hours or walk-in centre) • Exacerbations (defined as need for course of oral steroids) • Asthma control questionnaires (ACT; CACT; ACQ; PACQ; RCP-3) • QoL (AQLQ; pAQLQ; St George's respiratory questionnaire) Important outcomes: • Lung function (FEV1, PEF) • Symptoms (annual symptom free days) • Dose of regular asthma therapy / preventer medication (ICS dose) • Rescue medication (SABA use) • Time off school or work
Exclusions	• Exclude observational cohort studies and NRS unless limited evidence from RCTs • Studies not in English • Not occupational asthma /allergens
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	Stratify by age group Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Synthesis of data • Meta-analysis will be conducted where appropriate • Outcomes will be grouped into the following categories based on time-points: ○ <6 months (or the one nearest to 6 months if multiple time-points are given) ○ ≥6 months (or the longest one if multiple time-points are given) Default MIDs will be used where no MIDs are established: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes If no/insufficient evidence is found we will (in order of preference): • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Consider observational studies and NRS • Consider prognostic studies • Move to GC consensus
Analysis-subgroups	
Key papers	

C.18 Monitoring: FeNO

Table 18: Review protocol: FeNO to monitor asthma control

Component	Description
Review question	In people with asthma, what is the clinical and cost-effectiveness of using fractional exhaled nitric oxide (FeNO) measures for monitoring asthma control?
Objectives	To evaluate the clinical and cost-effectiveness of using fractional exhaled nitric oxide (FeNO) for monitoring asthma control?
Study design	• RCTs
Population / Target condition	People with asthma (defined as physician Dx with objective test). If insufficient evidence is found we will consider evidence from studies where asthma is defined as

	physician Dx only or on asthma treatment (give details of how Dx was made). Not including severe asthma. All ages, stratified into the following 2 different groups: • Children/young people (5-16 years old) • Adults (>16 years old) The following groups will be included/combined in the analysis (do not subgroup, would not make separate recommendations for these groups): • Smokers • Atopic asthma
Intervention	Monitoring FeNO and adjustment of management/therapy according to physician decision or personalised treatment plan (use of other interventions to be included if equal access in each group, eg both groups receive education in addition to monitoring) Only use validated methods of measuring FeNO (eg 50ml/s flow rate).
Comparison	Comparison of adjustment of asthma therapy based on FeNO to: • Usual care: eg clinical symptoms (with or without PEF) according to guidelines (including BTS/SIGN, GINA) • Asthma control questionnaires or QOL questionnaires • Lung function tests (spirometry or PEFv) • Blood eosinophils • Challenge tests Comparison of different frequencies of monitoring using FeNO.
Outcomes	Critical outcomes: • Mortality • Unscheduled healthcare utilisation (ED/A&E visit; hospital admissions; GP out of hours or walk-in centre) • Exacerbations (defined as need for course of oral steroids) • Asthma control questionnaires (ACT; CACT; ACQ; PACQ; RCP-3) • QoL (AQLQ; pAQLQ; St George's respiratory questionnaire) Important outcomes: • Lung function (FEV1, PEF) • Symptoms (annual symptom free days) • Dose of regular asthma therapy / preventer medication (ICS dose) • Rescue medication (SABA use) • Time off school or work
Exclusions	• Exclude observational cohort studies and NRS unless limited evidence from RCTs • Studies not in English • Not occupational asthma /allergens
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	Stratify by age group Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Synthesis of data • Meta-analysis will be conducted where appropriate • Outcomes will be grouped into the following categories based on time-points:

	○ <6 months (or the one nearest to 6 months if multiple time-points are given) ○ ≥6 months (or the longest one if multiple time-points are given) Default MIDs will be used where no MIDs are established: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes Sensitivity analysis: • SUBGROUP: if heterogeneity, subgroup according to the aim of the treatment in the study. Would expect different directions of effect in studies aiming to decrease ICS in controlled patients and studies aiming to increase ICS in uncontrolled patients. If no/insufficient evidence is found we will (in order of preference): • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Consider observational studies and NRS • Consider prognostic studies • Move to GC consensus
Analysis-subgroups to investigate heterogeneity	• SUBGROUP: if heterogeneity, subgroup according to the aim of the treatment in the study. Would expect different directions of effect in studies aiming to decrease ICS in controlled patients and studies aiming to increase ICS in uncontrolled patients.
Key papers	

C.19 Monitoring: Peripheral blood eosinophils

Table 19: Review protocol: Peripheral blood eosinophils to monitor asthma control

Component	Description
Review question	In people with asthma, what is the clinical and cost-effectiveness of using the peripheral blood eosinophil count for monitoring asthma control?
Objectives	To evaluate the clinical and cost-effectiveness of using peripheral blood eosinophil count for monitoring asthma control?
Study design	• RCTs
Population / Target condition	People with asthma (defined as physician Dx with objective test or recurrent persistent wheeze in <5 years). If insufficient evidence is found we will consider evidence from studies where asthma is defined as physician Dx only or on asthma treatment (give details of how Dx was made). Not including severe asthma. All ages, stratified into the following 3 different groups: • Children (1-<5 years old) • Children/young people (5-16 years old) • Adults (>16 years old) The following groups will be included/combined in the analysis (do not subgroup, would not make separate recommendations for these groups): • Smokers • Atopic asthma
Intervention	Monitoring peripheral blood eosinophil count and adjustment of management/therapy according to physician decision or personalised treatment plan (use of other interventions to be included if equal access in each group, eg both groups receive education in addition to monitoring).

Comparison	Comparison of adjustment of asthma therapy based on peripheral blood eosinophil count to: • Usual care: eg clinical symptoms (with or without PEF) according to guidelines (including BTS/SIGN, GINA) • Asthma control questionnaires or QOL questionnaires • Lung function tests (spirometry or PEFv) • Challenge tests Comparison of different frequencies of monitoring using blood eosinophil count.
Outcomes	Critical outcomes: • Mortality • Unscheduled healthcare utilisation (ED/A&E visit; hospital admissions; GP out of hours or walk-in centre) • Exacerbations (defined as need for course of oral steroids) • Asthma control questionnaires (ACT; CACT; ACQ; PACQ; RCP-3) • QoL (AQLQ; pAQLQ; St George's respiratory questionnaire) Important outcomes: • Lung function (FEV1, PEF) • Symptoms (annual symptom free days) • Dose of regular asthma therapy / preventer medication (ICS dose) • Rescue medication (SABA use) • Time off school or work
Exclusions	• Exclude observational cohort studies and NRS unless limited evidence from RCTs • Studies not in English • Not occupational asthma /allergens
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	Stratify by age group Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Synthesis of data • Meta-analysis will be conducted where appropriate • Outcomes will be grouped into the following categories based on time-points: ○ <6 months (or the one nearest to 6 months if multiple time-points are given) ○ ≥6 months (or the longest one if multiple time-points are given) Default MIDs will be used where no MIDs are established: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes If no/insufficient evidence is found we will (in order of preference): • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Consider observational studies and NRS • Consider prognostic studies • Move to GC consensus
Analysis-subgroups to	

investigate heterogeneity	
Key papers	

C.20 Monitoring: Challenge tests

Table 20: Review protocol: Challenge tests to monitor asthma control

Component	Description
Review question	In people with asthma, what is the clinical and cost-effectiveness of using indirect challenge tests with mannitol or direct challenge tests with histamine or methacholine for monitoring asthma control?
Objectives	To evaluate the clinical and cost-effectiveness of using indirect challenge tests with mannitol, or direct challenge tests with histamine or methacholine PC20 for monitoring asthma control?
Study design	• RCTs
Population / Target condition	People with asthma (defined as physician Dx with objective test). If insufficient evidence is found we will consider evidence from studies where asthma is defined as physician Dx only or on asthma treatment (give details of how Dx was made). Not including severe asthma. All ages, stratified into the following 2 different groups: • Children/young people (5-16 years old) • Adults (>16 years old)
Intervention	Monitoring using indirect or direct challenge tests and using the outcomes to adjust management/therapy according to physician decision or personalised treatment plan (use of other interventions to be included if equal access in each group, eg both groups receive education in addition to monitoring): • Indirect challenge test with mannitol • Direct challenge test with methacholine or histamine
Comparison	Comparison of adjustment of asthma therapy based on indirect or direct challenge tests to: • Usual care: eg clinical symptoms according to guidelines (including BTS/SIGN, GINA) • Asthma control questionnaires or QOL questionnaires • Lung function tests (spirometry or PEFv) Comparison of adjustment of asthma therapy based on: • Indirect vs direct challenge tests • Comparison of different frequencies of monitoring using challenge tests
Outcomes	Critical outcomes: • Mortality • Unscheduled healthcare utilisation (ED/A&E visit; hospital admissions; GP out of hours or walk-in centre) • Exacerbations (defined as need for course of oral steroids) • Asthma control questionnaires (ACT; CACT; ACQ; PACQ; RCP-3) • QoL (AQLQ; pAQLQ; St George's respiratory questionnaire) Important outcomes: • Lung function (FEV1, PEF) • Symptoms (annual symptom free days)

	• Dose of regular asthma therapy / preventer medication (ICS dose) • Rescue medication (SABA use) • Time off school or work
Exclusions	• Exclude observational cohort studies and NRS unless limited evidence from RCTs • Studies not in English • Not occupational asthma /allergens
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	Stratify by age group Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Synthesis of data • Meta-analysis will be conducted where appropriate • Outcomes will be grouped into the following categories based on time-points: ○ <6 months (or the one nearest to 6 months if multiple time-points are given) ○ ≥6 months (or the longest one if multiple time-points are given) Default MIDs will be used where no MIDs are established: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes If no/insufficient evidence is found we will (in order of preference): • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Consider observational studies and NRS • Consider prognostic studies • Move to GC consensus
Analysis-subgroups to investigate heterogeneity	
Key papers	

C.21 Monitoring: Adherence to treatment

Table 21: Review protocol: Monitoring adherence to treatment

Component	Description
Review question	In people with asthma, what is the clinical and cost-effectiveness of monitoring adherence to treatment?
Objectives	To evaluate the clinical and cost-effectiveness of monitoring adherence to treatment? Adherence with repeat therapies
Study design	• RCTs
Population / Target condition	People with asthma (defined as physician Dx with objective test or recurrent persistent wheeze in <5 years). If insufficient evidence is found we will consider evidence from studies where asthma is defined as physician Dx only or on asthma treatment (give details of how Dx was made). Not including severe asthma. All ages, stratified into the following 3 different groups: • Children (1-<5 years old) • Children/young people (5-16 years old)

	• Adults (>16 years old)
Intervention	Monitoring adherence/compliance/concordance using the following methods and provide patient feedback or intervention to improve adherence (use of other interventions to be included if equal access in each group, eg both groups receive education in addition to monitoring): • Adherence with repeat therapy (using prescription and refill data) • Electronic monitoring inhalers (to monitor inhaler use) • Prednisolone levels (serum and urine – when on prednisolone) • MARS questionnaire (medication adherence rating scale) • FeNO levels (comes down if patients are taking their inhalers) • Theophylline levels (when on theophylline)
Comparison	• No monitoring of adherence • Usual care • Comparison of different frequencies of monitoring adherence
Outcomes	Critical outcomes: • Mortality • Unscheduled healthcare utilisation (ED/A&E visit; hospital admissions; GP out of hours or walk-in centre) • Exacerbations (defined as need for course of oral steroids) • Asthma control questionnaires (ACT; CACT; ACQ; PACQ; RCP-3) • QoL (AQLQ; pAQLQ; St George's respiratory questionnaire) • Adherence Important outcomes: • Lung function (FEV1, PEF) • Symptoms (annual symptom free days) • Dose of regular asthma therapy / preventer medication (ICS dose) • Rescue medication (SABA use) • Time off school or work
Exclusions	• Exclude observational cohort studies and NRS unless limited evidence from RCTs • Studies not in English • Not occupational asthma /allergens
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Search terms	• Adherence • Compliance • Concordance
Review Strategy	Stratify by age group Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Synthesis of data • Meta-analysis will be conducted where appropriate • Outcomes will be grouped into the following categories based on time-points: ○ <6 months (or the one nearest to 6 months if multiple time-points are given) ○ ≥6 months (or the longest one if multiple time-points are given) Default MIDs will be used where no MIDs are established: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes If no/insufficient evidence is found we will (in order of preference):

	• Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Consider observational studies and NRS • Consider prognostic studies • Move to GC consensus
Analysis-subgroups to investigate heterogeneity	• Socio economic disadvantage • Cognitive function • Some ethnic groups • Disability (esp. use of inhalers) • Near fatal asthma attacks (associated with psychological effects etc)

C.22 Monitoring: Inhaler technique

Table 22: Review protocol: Monitoring inhaler technique

Component	Description
Review question	In people with asthma, what is the optimal frequency and method for monitoring inhaler technique?
Objectives	To evaluate the clinical and cost-effectiveness of the optimal frequency and method for monitoring inhaler technique?
Study design	• RCTs
Population / Target condition	People with asthma (defined as physician Dx with objective test or recurrent persistent wheeze in <5 years). If insufficient evidence is found we will consider evidence from studies where asthma is defined as physician Dx only or on asthma treatment (give details of how Dx was made). Not including severe asthma. All ages, stratified into the following 3 different groups: • Children (1-<5 years old) • Children/young people (5-16 years old) • Adults (>16 years old)
Intervention	Monitoring inhaler technique using the following methods and provide patient feedback or intervention to improve inhaler technique (use of other interventions to be included if equal access in each group, eg both groups receive education in addition to monitoring): • Electronic devices to monitor inhaler technique (devices check the inhaler is being used correctly but this will still be face-to-face monitoring) • Visual monitoring by doctor, nurse or pharmacist (may include use of a checklist to monitor inhaler technique)
Comparison	• No monitoring of inhaler technique • Comparison of different frequencies of monitoring inhaler technique • Monitoring using electronic devices vs monitoring by visual inspection
Outcomes	Critical outcomes: • Mortality • Unscheduled healthcare utilisation (ED/A&E visit; hospital admissions; GP out of hours or walk-in centre) • Exacerbations (defined as need for course of oral steroids) • Asthma control questionnaires (ACT; CACT; ACQ; PACQ; RCP-3) • QoL (AQLQ; pAQLQ; St George's respiratory questionnaire) Important outcomes: • Lung function (FEV1, PEF)

	• Symptoms (annual symptom free days) • Dose of regular asthma therapy / preventer medication (ICS dose) • Rescue medication (SABA use) • Time off school or work
Exclusions	• Exclude observational cohort studies and NRS unless limited evidence from RCTs • Studies not in English • Not occupational asthma /allergens
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	Stratify by age group Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Synthesis of data • Meta-analysis will be conducted where appropriate • Outcomes will be grouped into the following categories based on time-points: ○ <6 months (or the one nearest to 6 months if multiple time-points are given) ○ ≥6 months (or the longest one if multiple time-points are given) Default MIDs will be used where no MIDs are established: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes If no/insufficient evidence is found we will (in order of preference): • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Consider observational studies and NRS • Consider prognostic studies • Move to GC consensus
Analysis-subgroups to investigate heterogeneity	
Key papers	

C.23 Monitoring: Tele-healthcare

Table 23: Review protocol: Tele-healthcare to monitor asthma control

Component	Description
Review question	In people with asthma, what is the clinical and cost-effectiveness of tele-healthcare to monitor asthma control?
Objectives	To review the efficacy and effectiveness of tele-healthcare to monitor asthma control.
Study design	Full reports of randomised controlled trials which compared a tele-healthcare intervention with usual care or any other control intervention.
Population	Children and adults with clinician-diagnosed asthma. We included studies conducted in both primary and secondary care settings. We focused on studies which looked exclusively at people with asthma. There were no exclusions on the basis of age, gender, ethnicity or language spoken.
Intervention and comparison	Focus on the proactive use of ICT to provide the information the health professional requires to make their decisions and then feedback of their advice to the patient. The study of technology needed to be central and its use sustained. These interventions included the following. • Video or telephone links between patient and healthcare professionals in real time or using store-and-forward technologies. • Systems of care using Internet-based telecommunication; these could be synchronous or asynchronous (e.g. Skype®, messaging, email) with healthcare professionals. • Systems of care using both wired and wireless telemetry for monitoring of Peak Expiratory Flow (PEF), spirometry (Forced Expiratory Volume in 1 second (FEV1); Forced Vital Capacity (FVC) respiratory rate, chest movement and oxygen saturations involving feedback to the patient, which had been processed or authorised by a healthcare professional. • Other systems of remote healthcare incorporating patient self-reporting of symptoms on a questionnaire and information exchange with a professional. • Complex intervention studies, if it was possible to tease out the individual tele-healthcare elements. Professional involvement in care was considered fundamentally important; we thus excluded the following types of interventions. • Remote interventions that were merely educational and so did not include the input of a professional, e.g. electronic information provision in an emergency waiting room. Although this type of passive information provision was excluded, education could have been part of a more complex interactive intervention that might fit the inclusion criteria, e.g. if it included feedback from a professional. • Decision support which functioned without the active input of a healthcare professional. •
Outcomes	Critical outcomes: • Mortality • Unscheduled healthcare utilisation (ED/A&E visit; hospital admissions; GP out of hours or walk-in centre) • Exacerbations (defined as need for course of oral steroids) • Asthma control questionnaires (ACT; CACT; ACQ; PACQ; RCP-3) • QoL (AQLQ; pAQLQ; St George's respiratory questionnaire) Important outcomes: • Lung function (FEV1, PEF) Symptoms (annual symptom free days)

Search	Trials were identified using the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED, and PsycINFO, and hand-searching of respiratory journals and meeting abstracts. All records coded as 'asthma' were searched using the following terms: Telehealth* or tele-health* or telemedicine*¬ or tele-medicine* or internet* or computer* or web* or interactive* or telecommunication* or telephone or phone or SMS or tele-monitor* or telemonitor* or telemanagement or tele-management¬ or teleconsultation or tele-consultation or telecare* or tele-care* or telematic* or telepharmacy or tele-pharmacy or telenurs* or tele-nurs* or video or email or e-mail or "remote consult*" or wireless or Bluetooth or tele-homecare or telehomecare or "remote care" or tele-support or telesupport or "mobile healthcare" or "computer mediated therapy" or ehealth or e-health or mhealth or m-health
Review strategy	Stratify by age group Appraisal of methodological quality • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. Synthesis of data • Meta-analysis will be conducted where appropriate Sources of potential heterogeneity will be assessed with subgroup analyses for device (phonecalls, SMS, email, internet software) and study length (<6 months and > 6 months), or summarised narratively where insufficient numbers of studies are found. Default MIDs will be used where no MIDs are established: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes

C.24 Health economic review protocols for all review questions

Review question	All questions – health economic evidence
Objectives	To identify economic evaluations relevant to the review questions set out above.
Criteria	• Populations, interventions and comparators must be as specified in the individual review protocols above. • Studies must be of a relevant economic study design (cost–utility analysis, cost–benefit analysis, cost-effectiveness analysis, cost–consequence analysis, comparative cost analysis). • Studies must not be an abstract only, a letter, editorial or commentary, or a review of economic evaluations.[(a)] Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	An economic study search will be undertaken using population-specific terms and an economic study filter – see Appendix F.
Review strategy	Each study fulfilling the criteria above will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in Appendix G of the NICE guidelines manual (2012).[1204] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. An economic evidence table will be completed and it will be included in the economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will

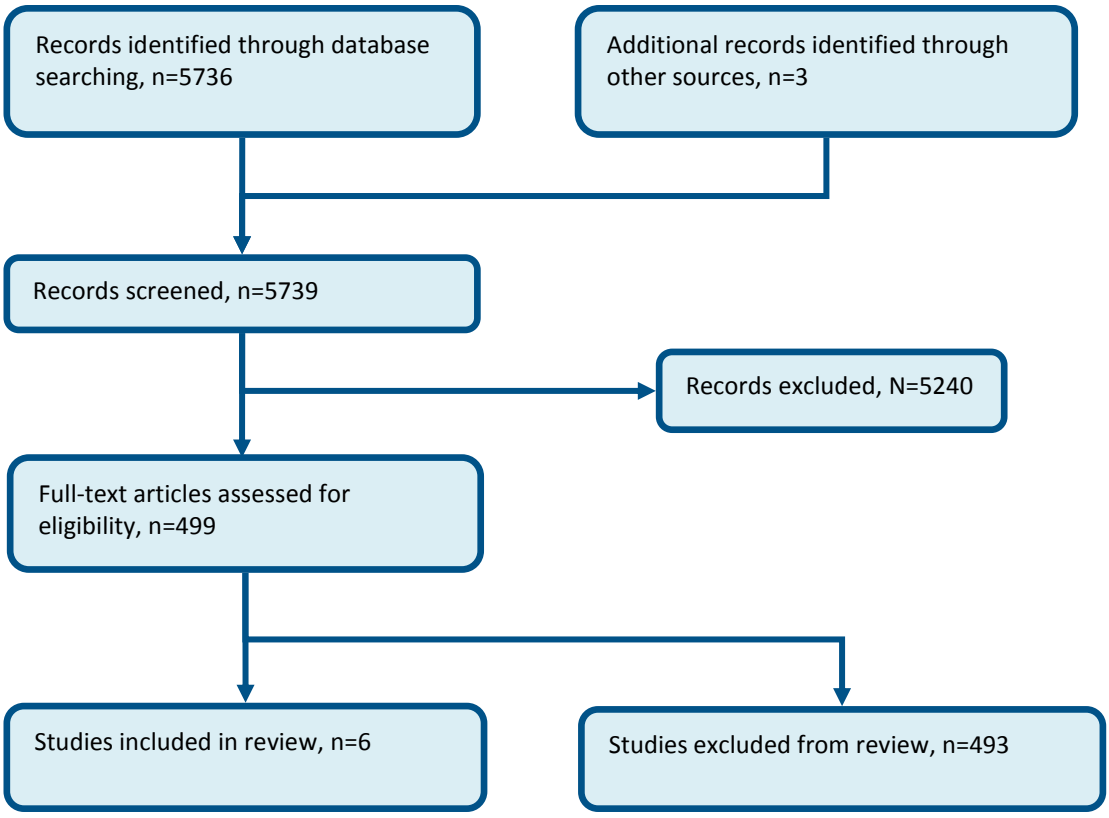
	usually be excluded from the guideline. If it is excluded then an economic evidence table will not be completed and it will not be included in the economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the GC if required. The ultimate aim is to include studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the GC if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded economic studies in Appendix H. The health economist will be guided by the following hierarchies. *Setting*: • UK NHS • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden) • OECD countries with predominantly private health insurance systems (for example, USA, Switzerland) • non-OECD settings (always 'Not applicable'). *Economic study type*: • cost–utility analysis • other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequence analysis) • comparative cost analysis • non-comparative cost analyses including cost-of-illness studies (always 'Not applicable'). • Year of analysis: • The more recent the study, the more applicable it is. *Quality and relevance of effectiveness data used in the economic analysis*: • The more closely the effectiveness data used in the economic analysis matches with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

(a) Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.

Appendix D: Clinical article selection

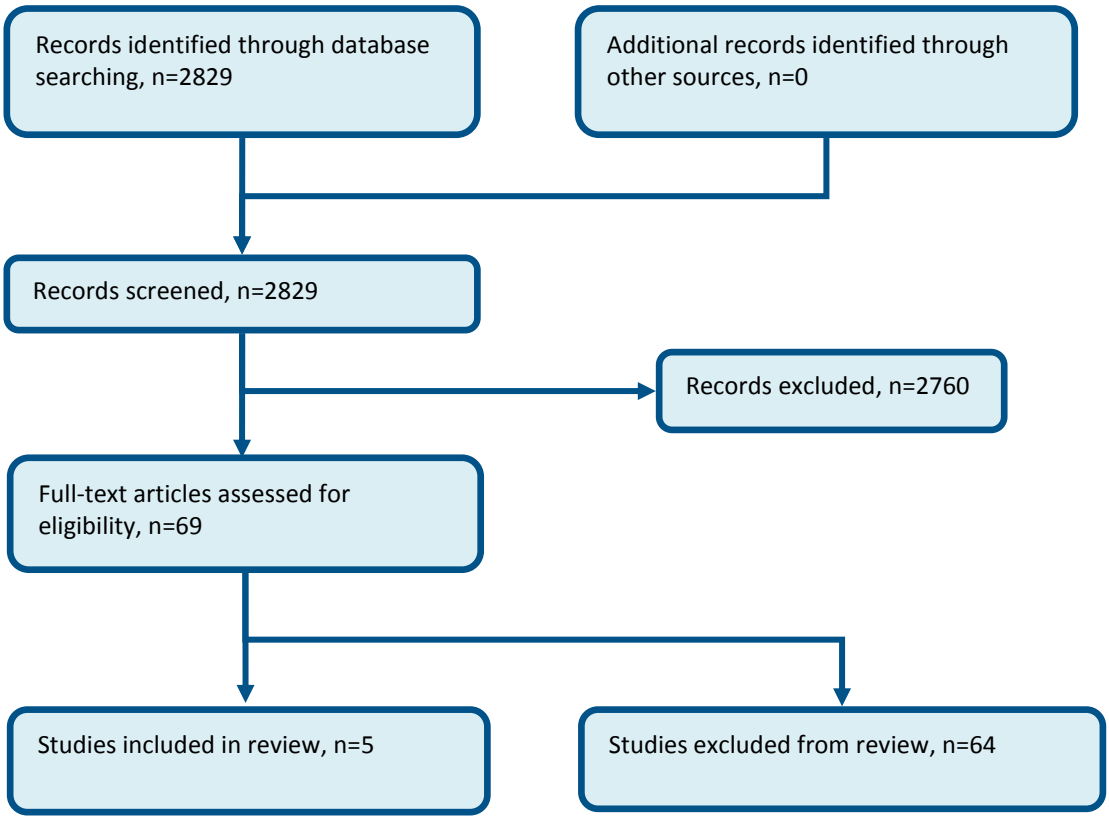
D.1 Diagnosis: Signs and symptoms

Figure 1: Flow diagram of article selection for the review of signs and symptoms



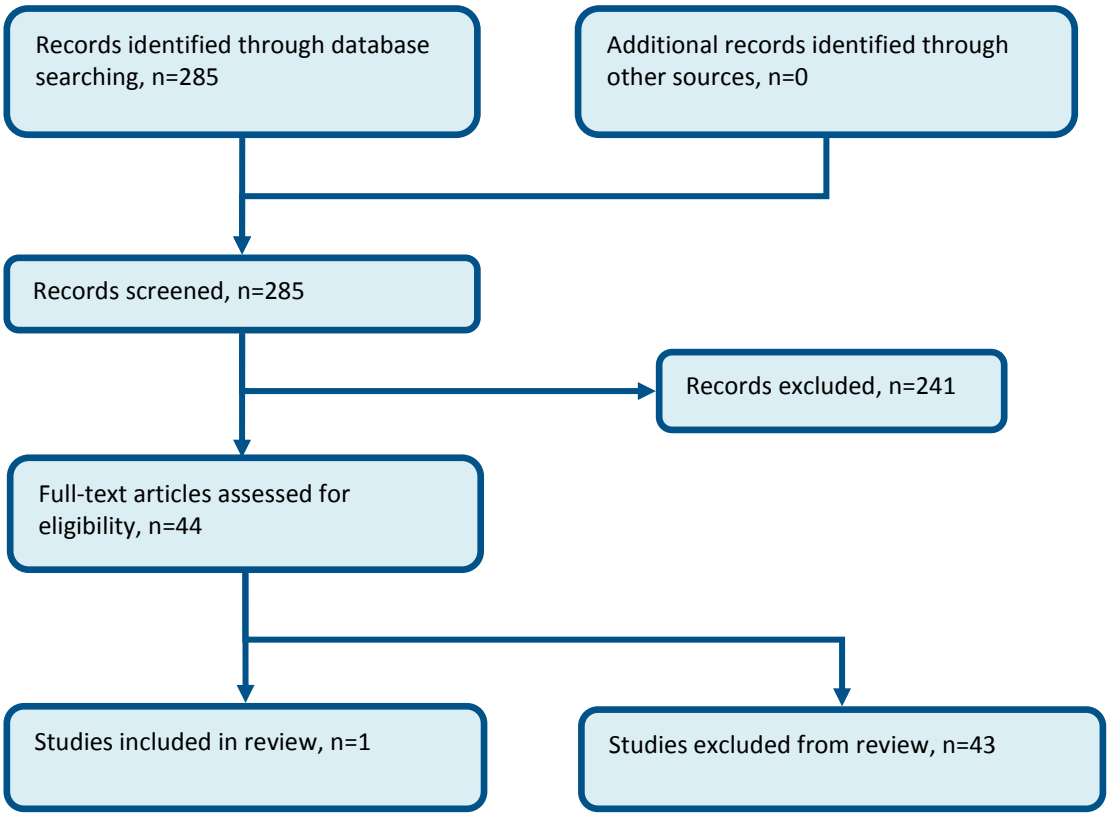
D.2 Diagnosis: History of atopic disorders

Figure 2: Flow diagram of clinical article selection for the review of history of atopic disorders



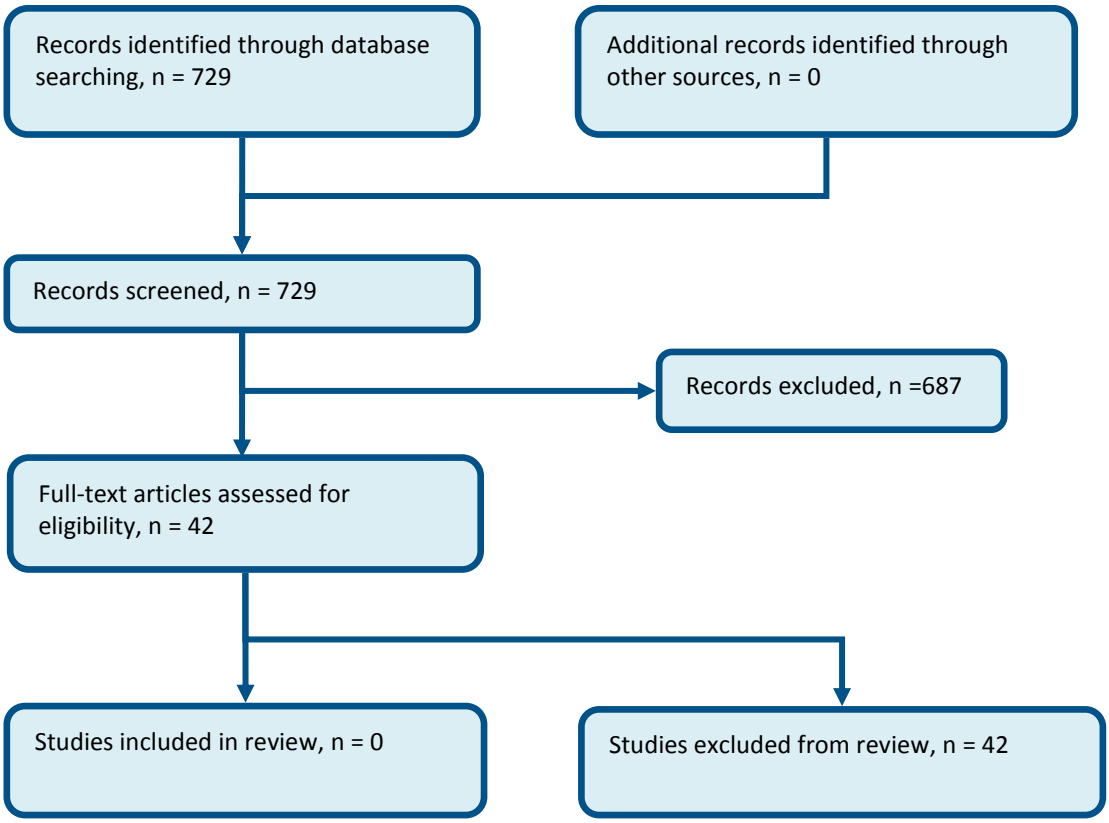
D.3 Diagnosis: Symptoms after exercise

Figure 3: Flow diagram of clinical article selection for the review of symptoms after exercise



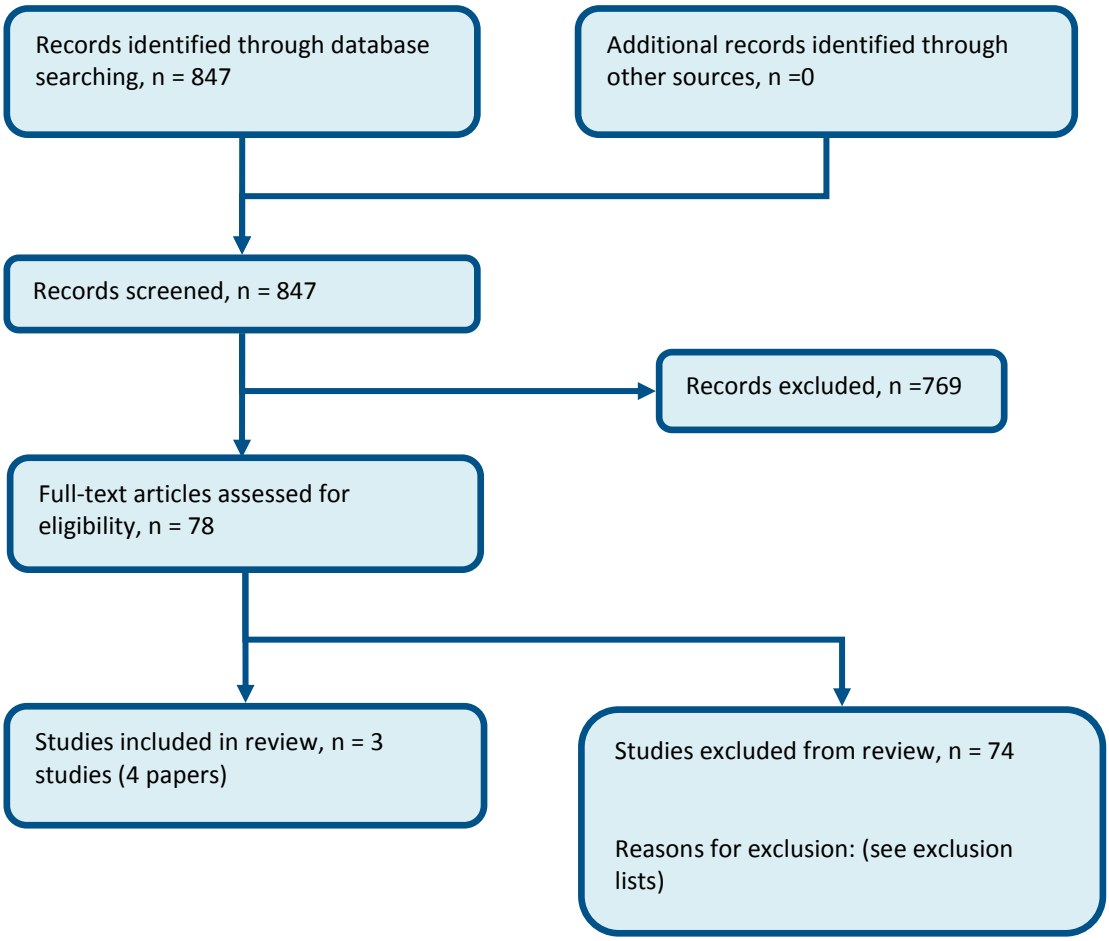
D.4 Diagnosis: Symptoms after using medication

Figure 4: Flow diagram of clinical article selection for the review of symptoms after using medication



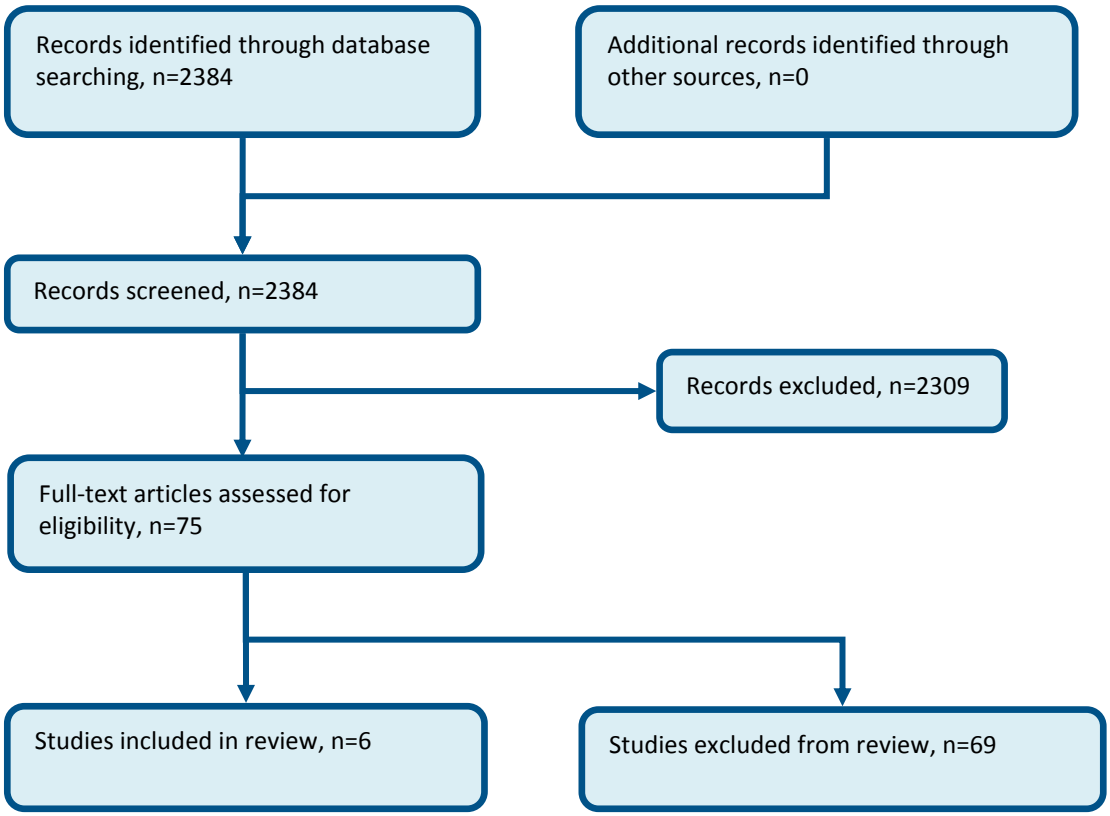
D.5 Diagnosis: Occupational asthma

Figure 5: Flow diagram of clinical article selection for the review of occupational asthma



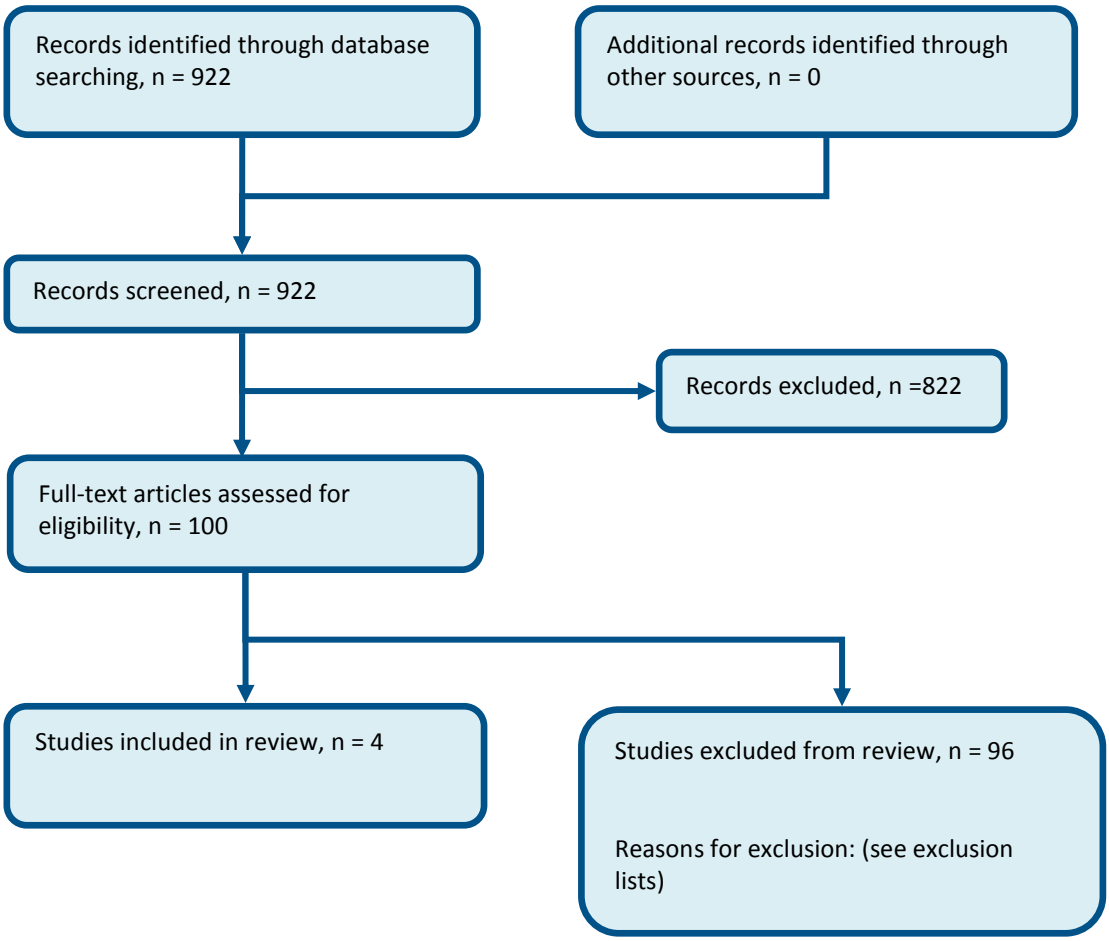
D.6 Diagnosis: Spirometry

Figure 6: Flow diagram of clinical article selection for the review of spirometry



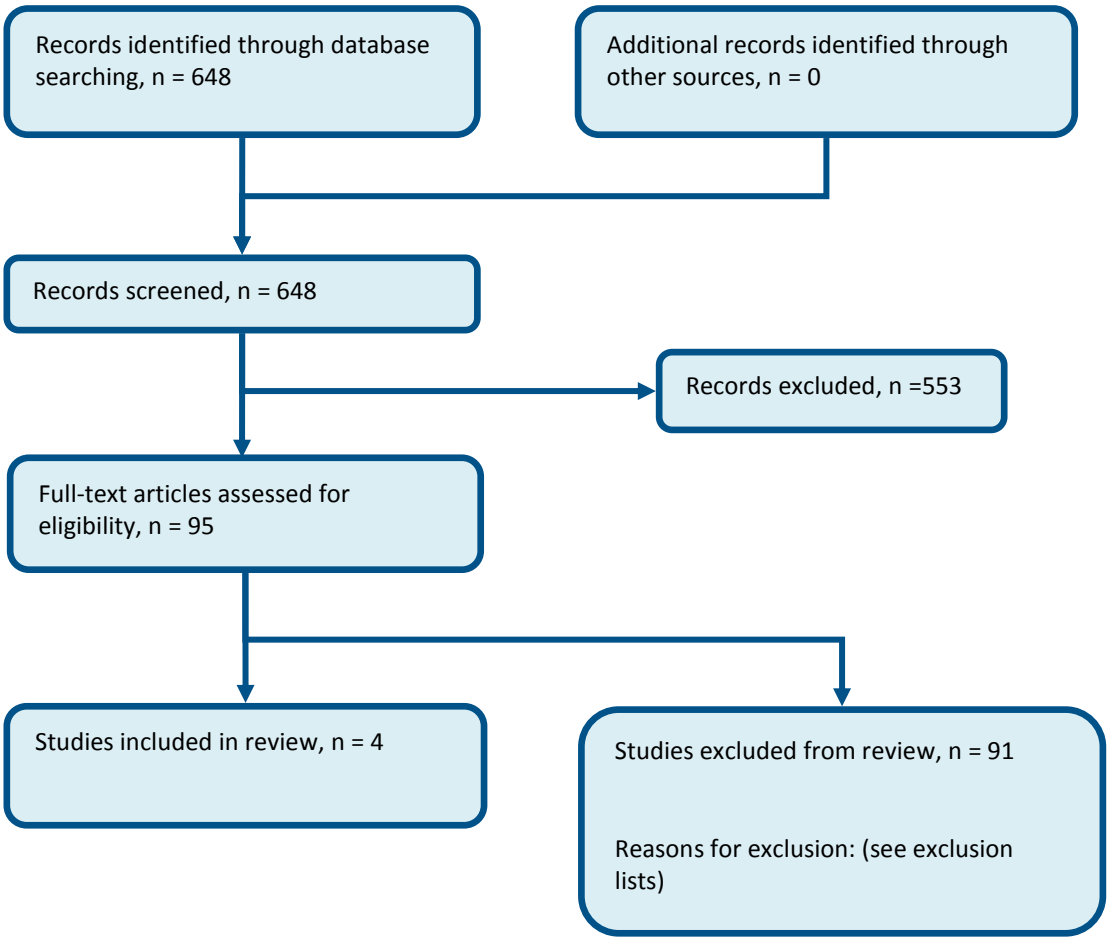
D.7 Diagnosis: Bronchodilator reversibility

Figure 7: Flow diagram of clinical article selection for the review of bronchodilator reversibility



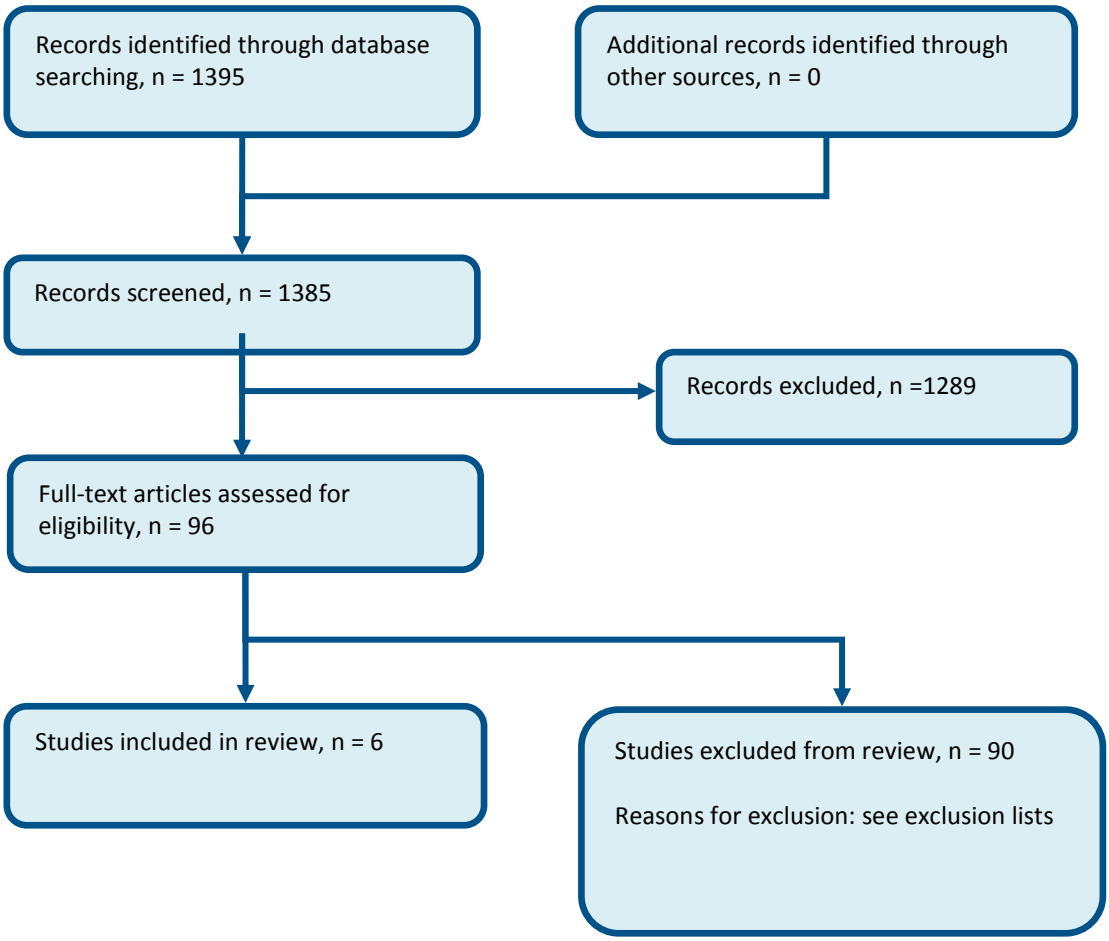
D.8 Diagnosis: PEF variability

Figure 8: Flow diagram of clinical article selection for the review of PEF variability



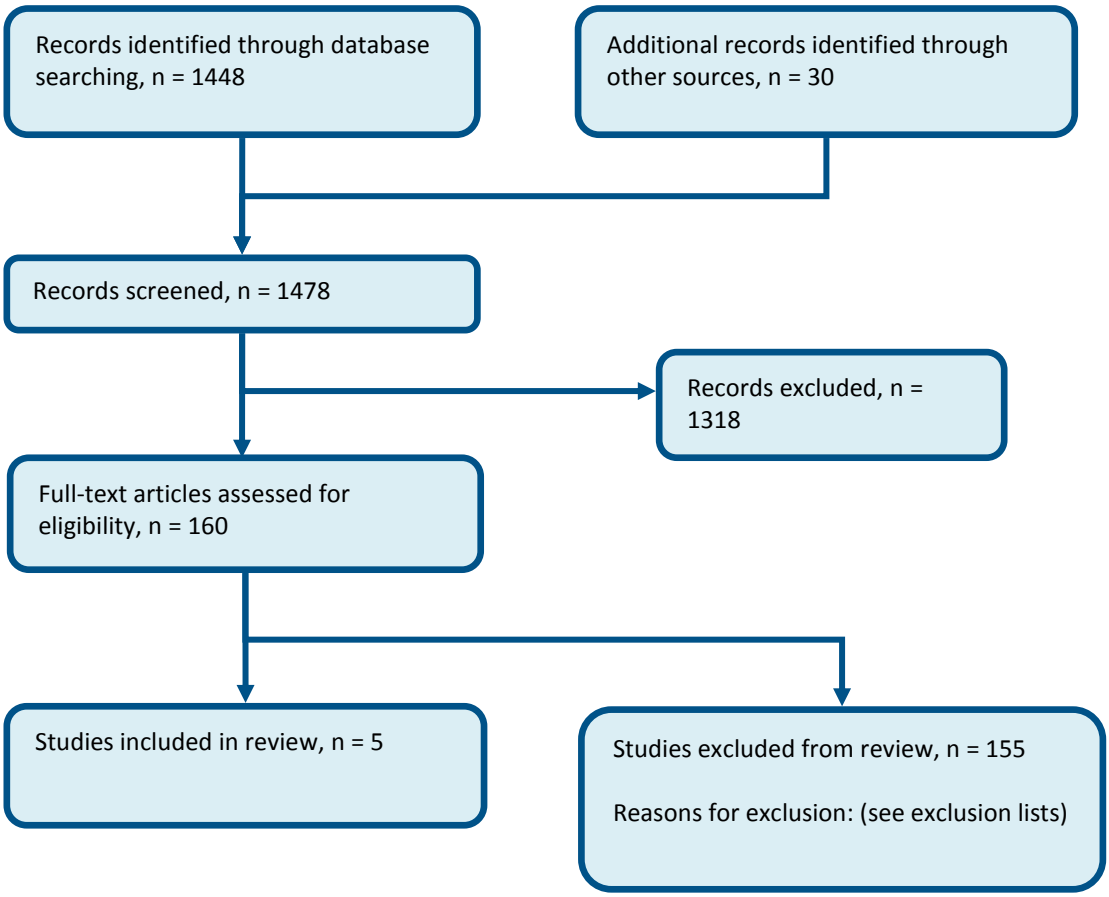
D.9 Diagnosis: Skin prick tests

Figure 9: Flow diagram of clinical article selection for the review of skin prick tests



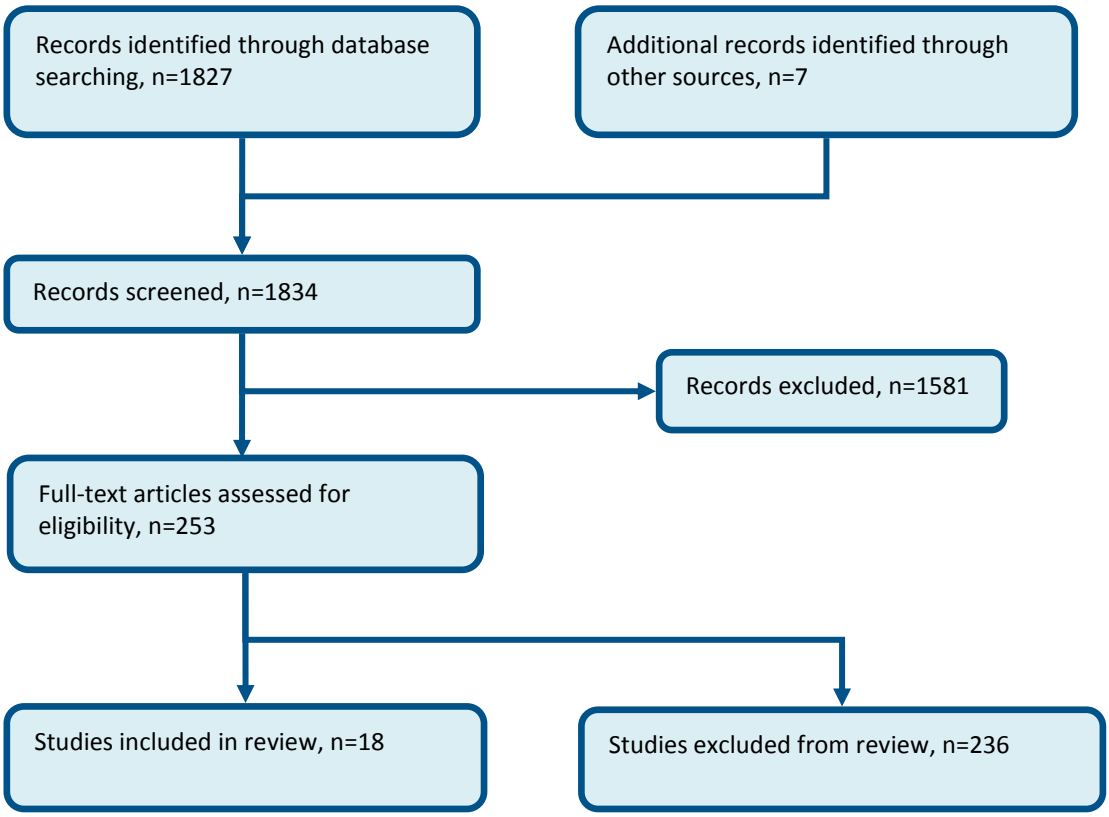
D.10 Diagnosis: IgE

Figure 10: Flow diagram of clinical article selection for the review of IgE



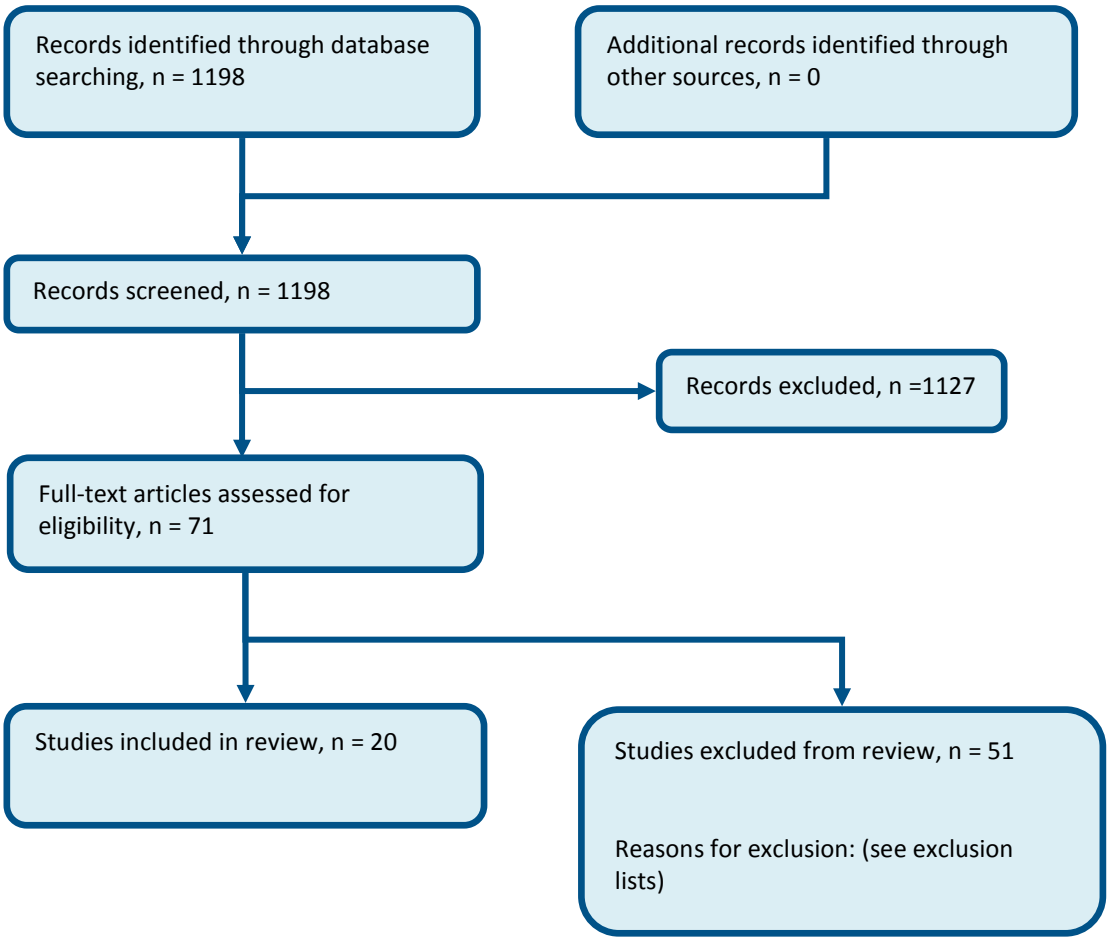
D.11 Diagnosis: FeNO

Figure 11: Flow diagram of article selection for the review of FeNO



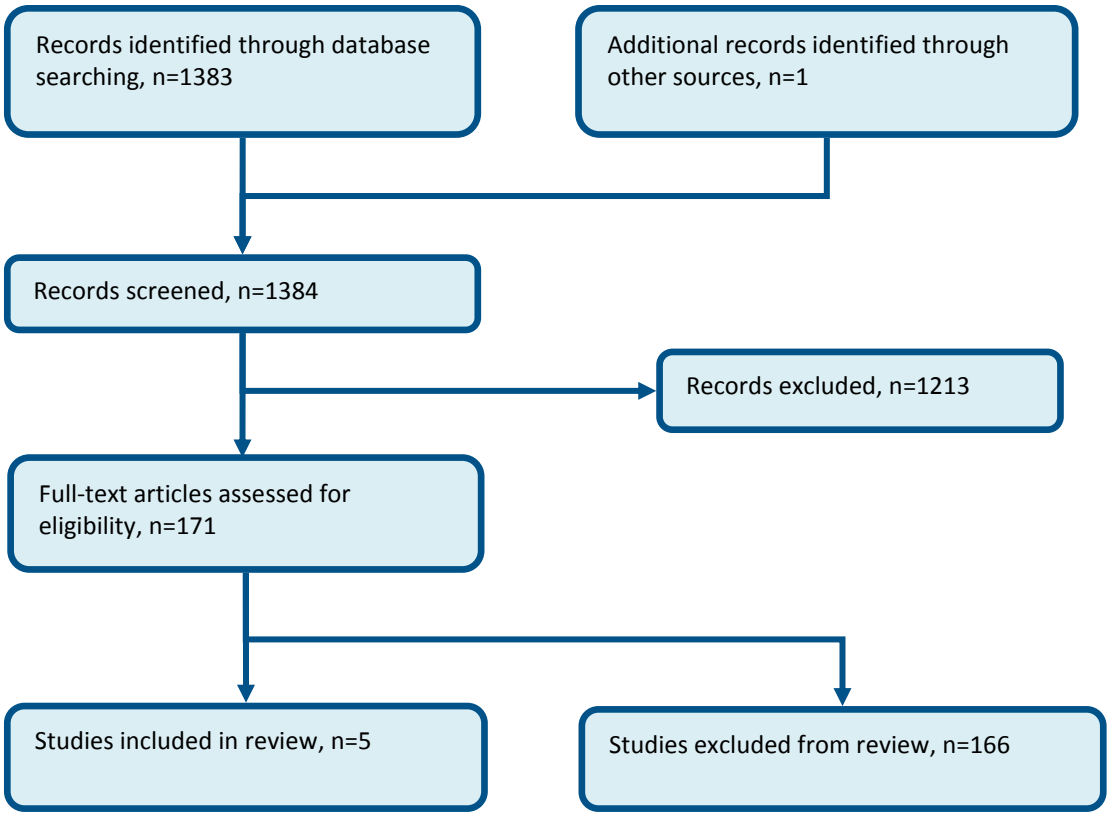
D.12 Diagnosis: Eosinophils

Figure 12: Flow diagram of clinical article selection for the review of peripheral blood eosinophils



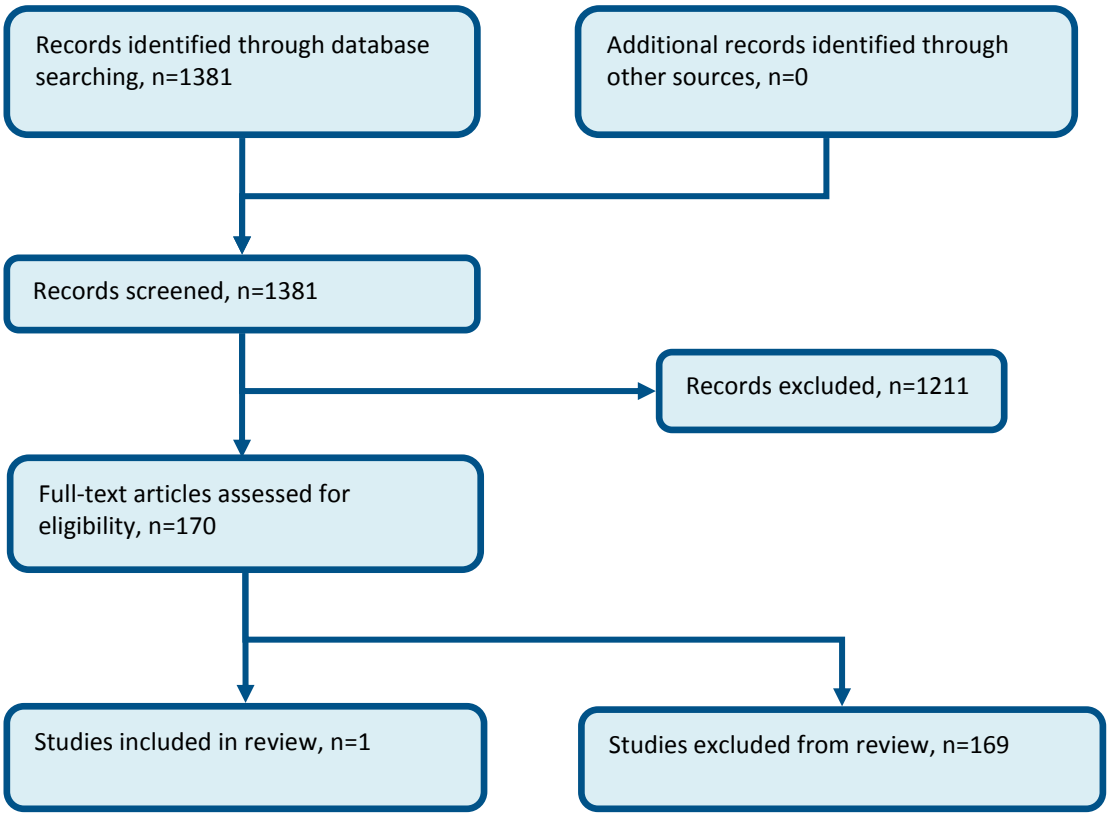
D.13 Diagnosis: Histamine and methacoline

Figure 13: Flow diagram of clinical article selection for the review of histamine and methacholine challenge tests



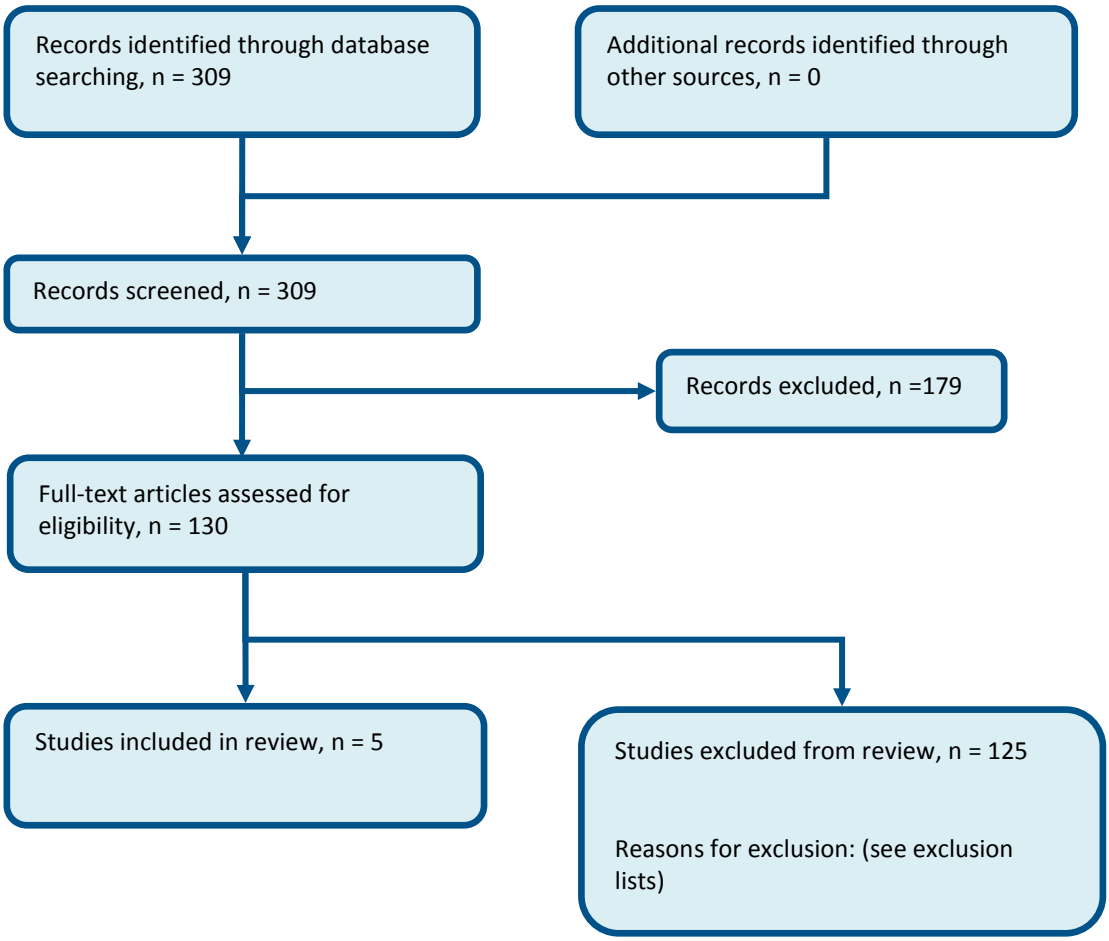
D.14 Diagnosis: Mannitol

Figure 14: Flow diagram of clinical article selection for the review of mannitol challenge test



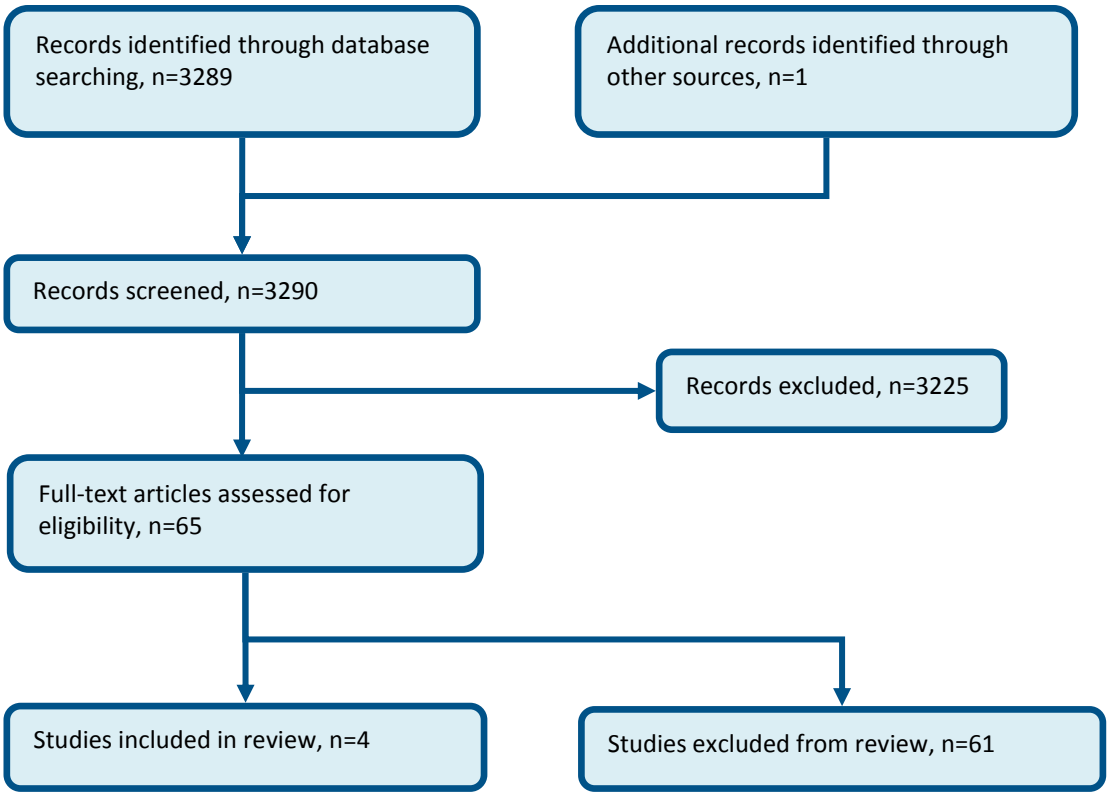
D.15 Diagnosis: Exercise

Figure 15: Flow diagram of clinical article selection for the review of exercise challenge test



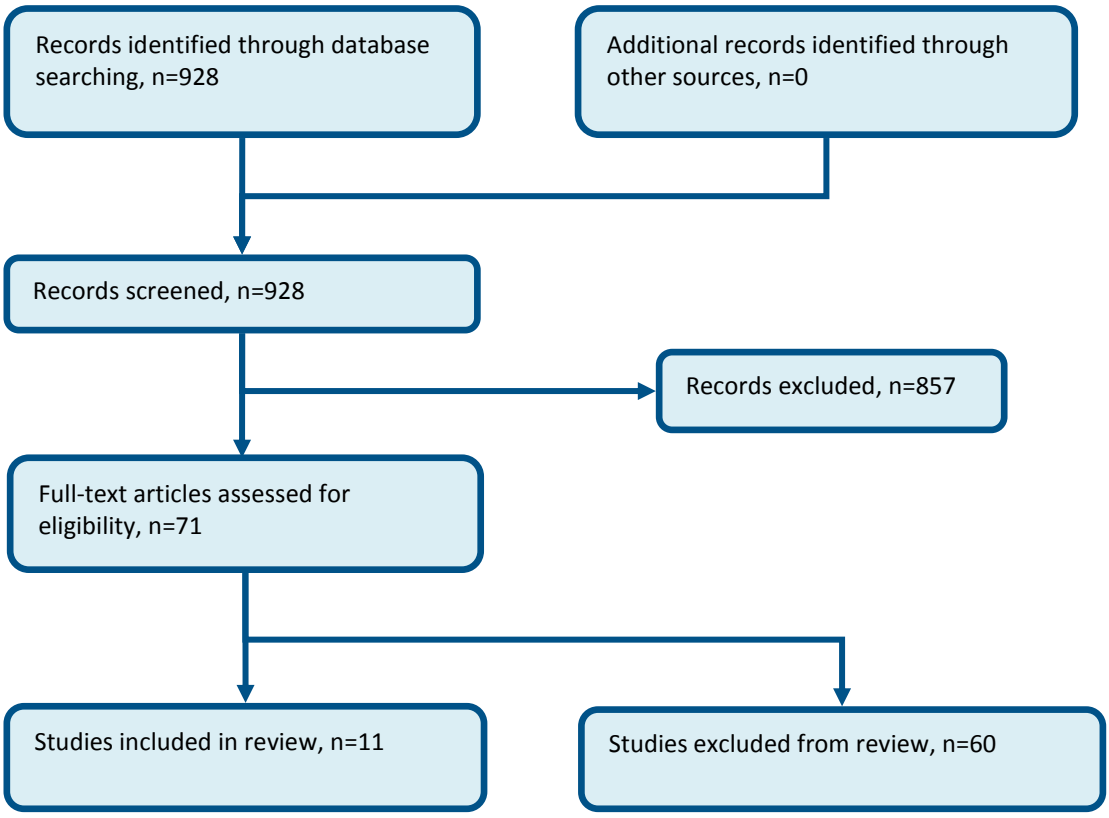
D.16 Monitoring: Questionnaires

Figure 16: Flow chart of clinical article selection for the review of symptom scores/diaries or validated questionnaires to monitor asthma control



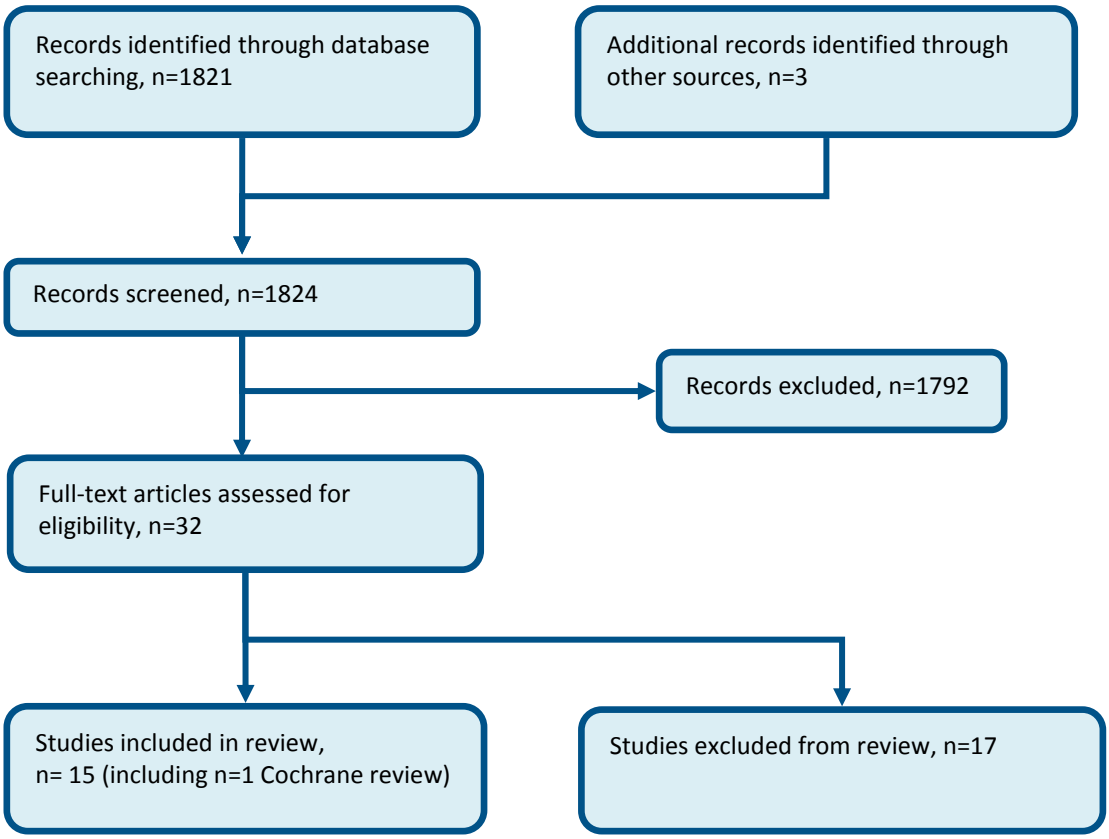
D.17 Monitoring: Lung function tests

Figure 17: Flow chart of clinical article selection for the review of lung function tests to monitor asthma control



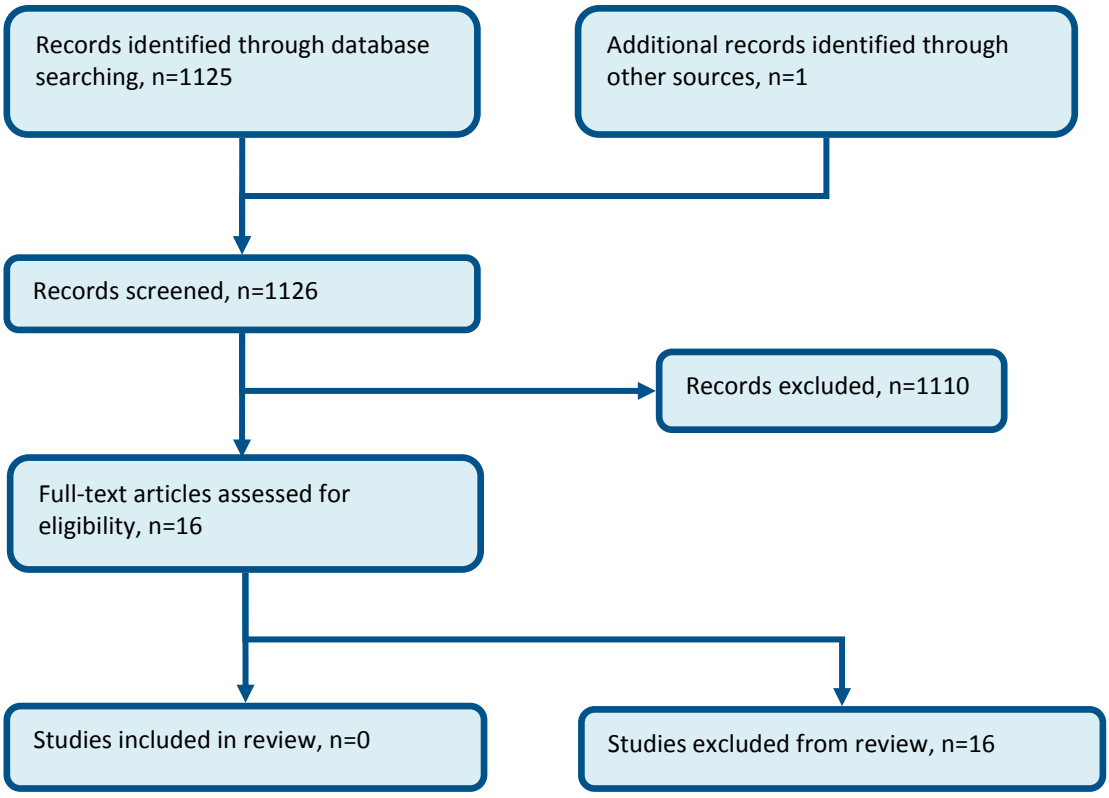
D.18 Monitoring: FeNO

Figure 18: Flow chart of clinical article selection for the review of FeNO to monitor asthma control



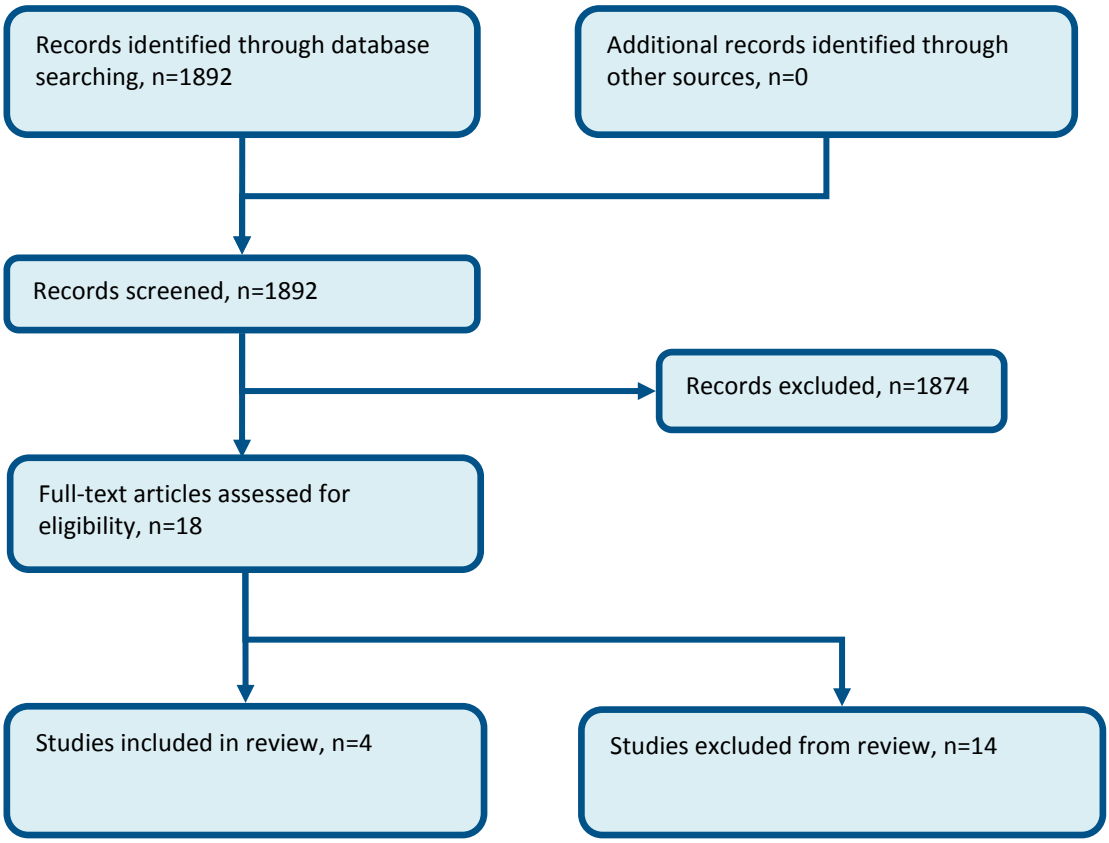
D.19 Monitoring: Peripheral blood eosinophils

Figure 19: Flow chart of clinical article selection for the review of peripheral blood eosinophils to monitor asthma control



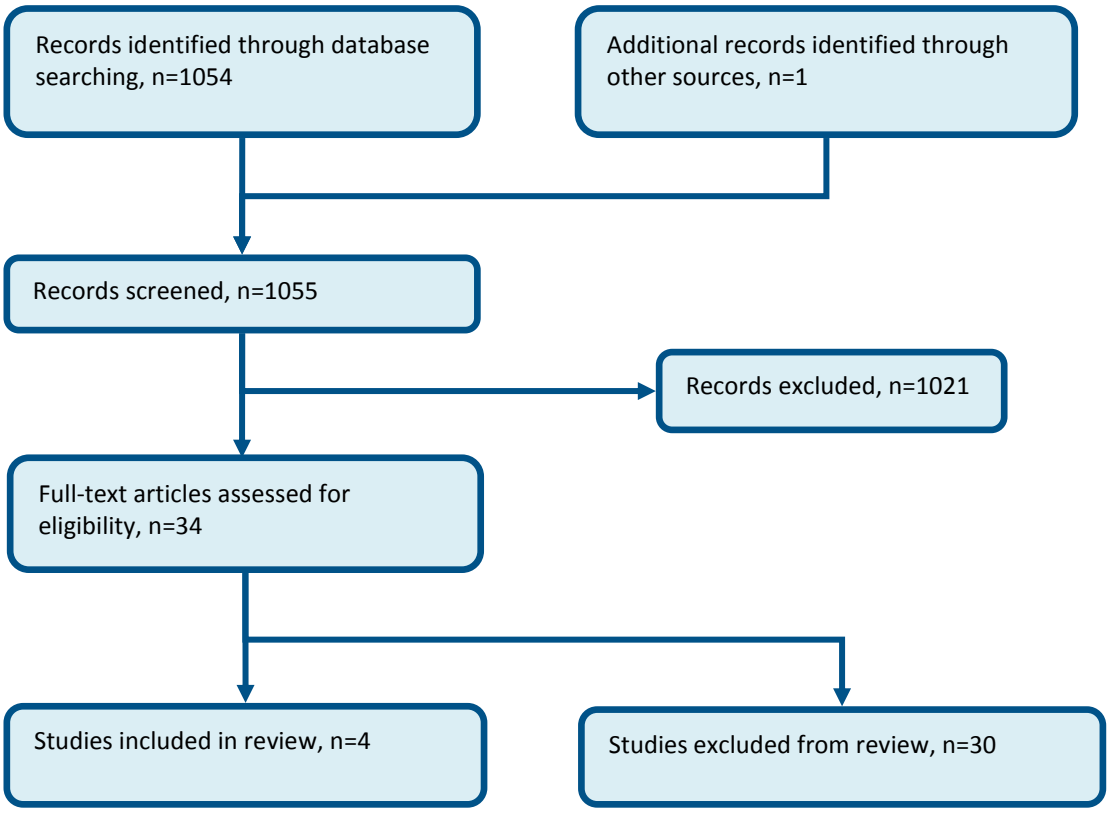
D.20 Monitoring: Challenge tests

Figure 20: Flow chart of clinical article selection for the review of challenge tests to monitor asthma control



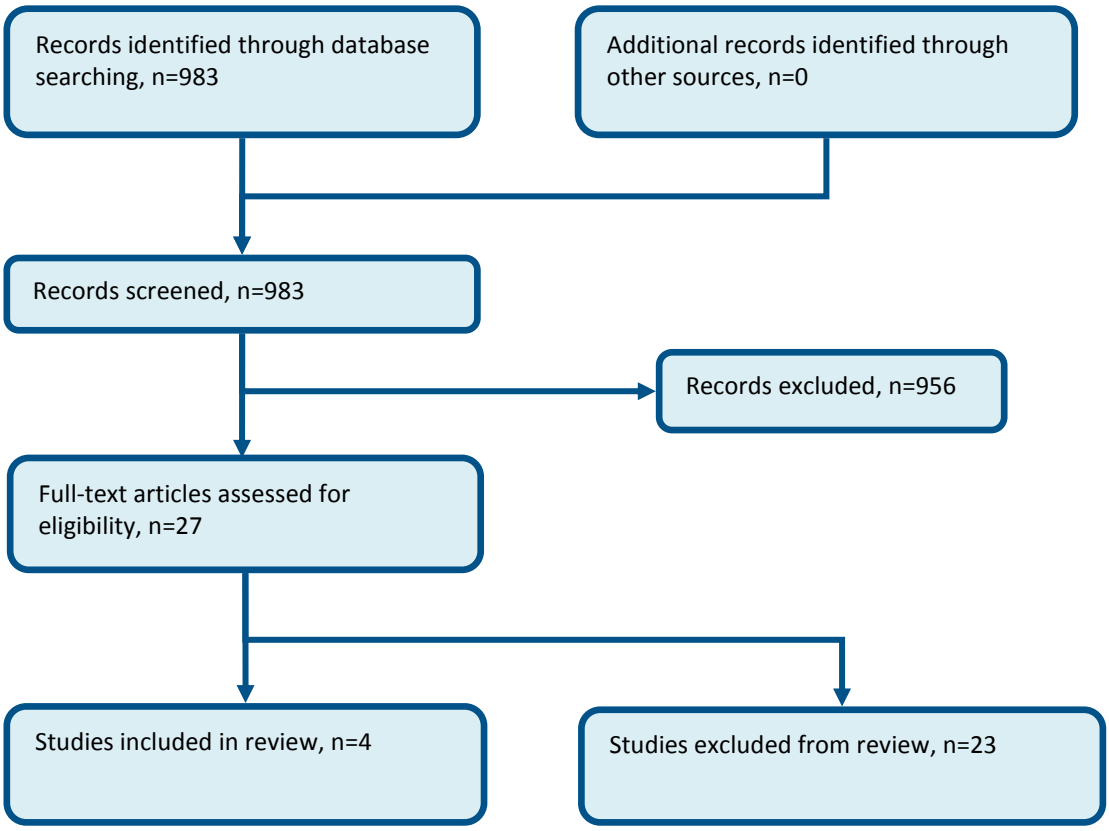
D.21 Monitoring: Adherence to treatment

Figure 21: Flow chart of clinical article selection for the review of monitoring adherence to treatment



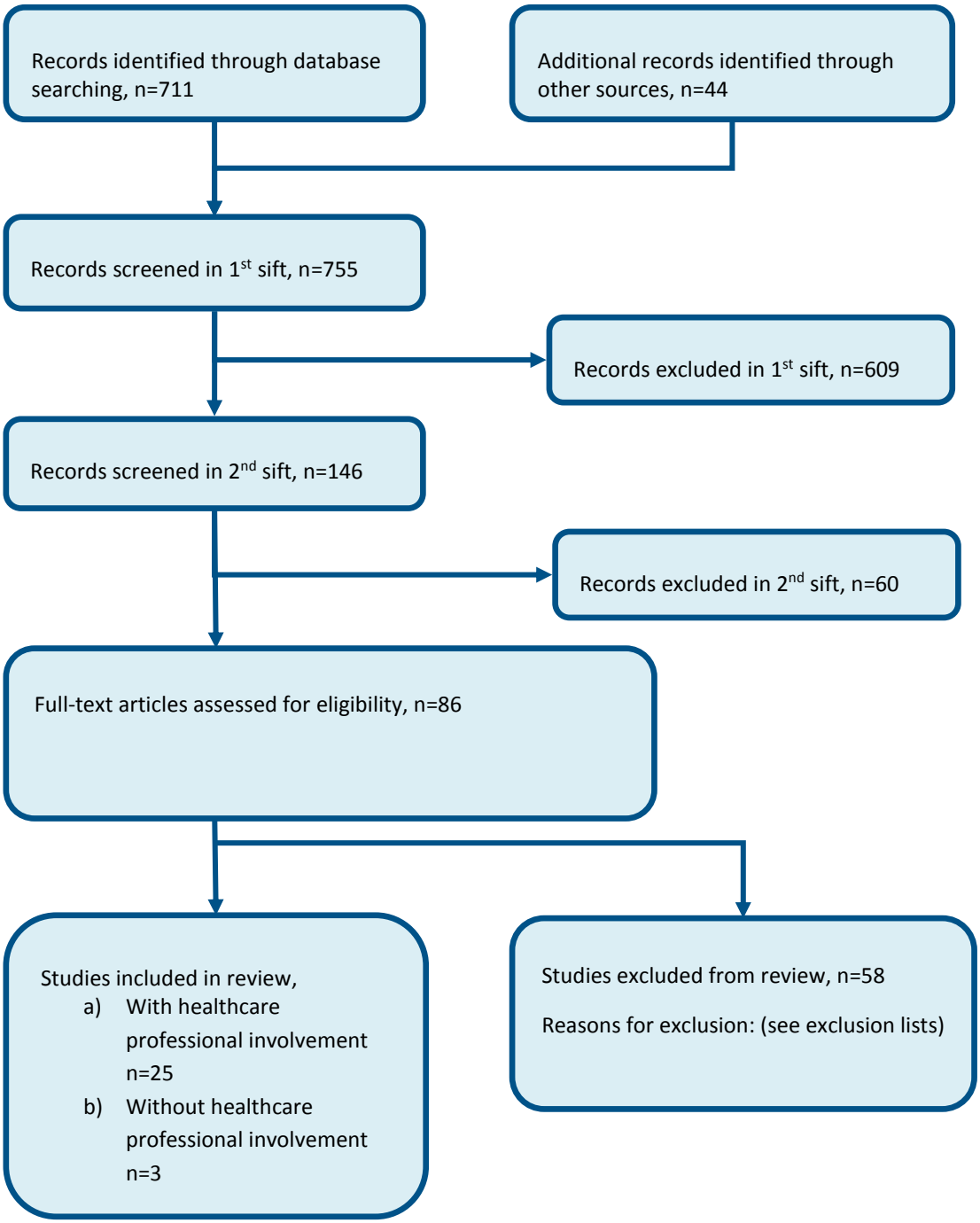
D.22 Monitoring: Inhaler technique

Figure 22: Flow chart of clinical article selection for the review of monitoring inhaler technique



D.23 Monitoring: Tele-healthcare

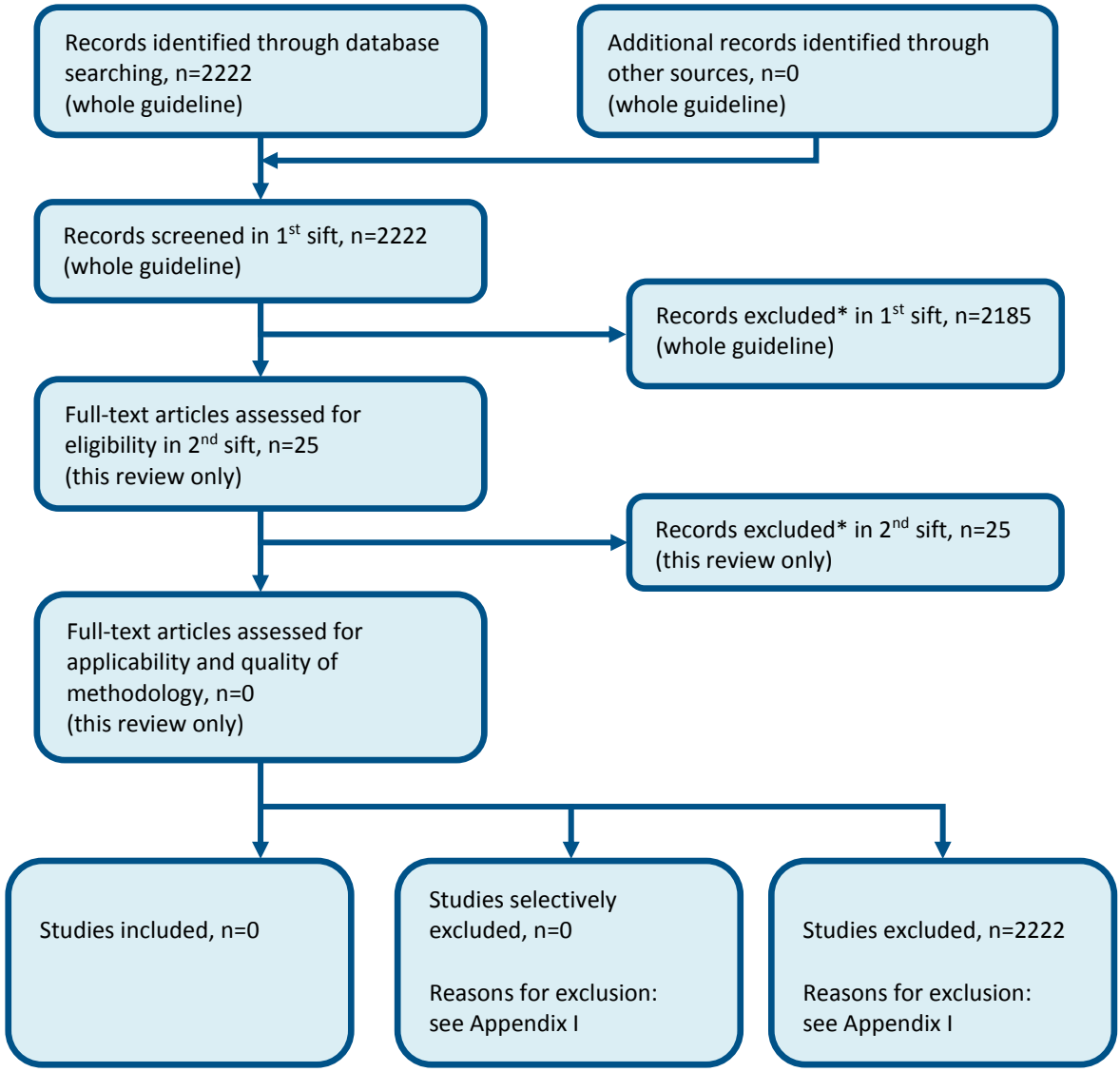
Figure 23: Flow chart of clinical article selection for the review of tele-healthcare to monitor asthma control



Appendix E: Economic article selection

E.1 Diagnosis: Signs and symptoms

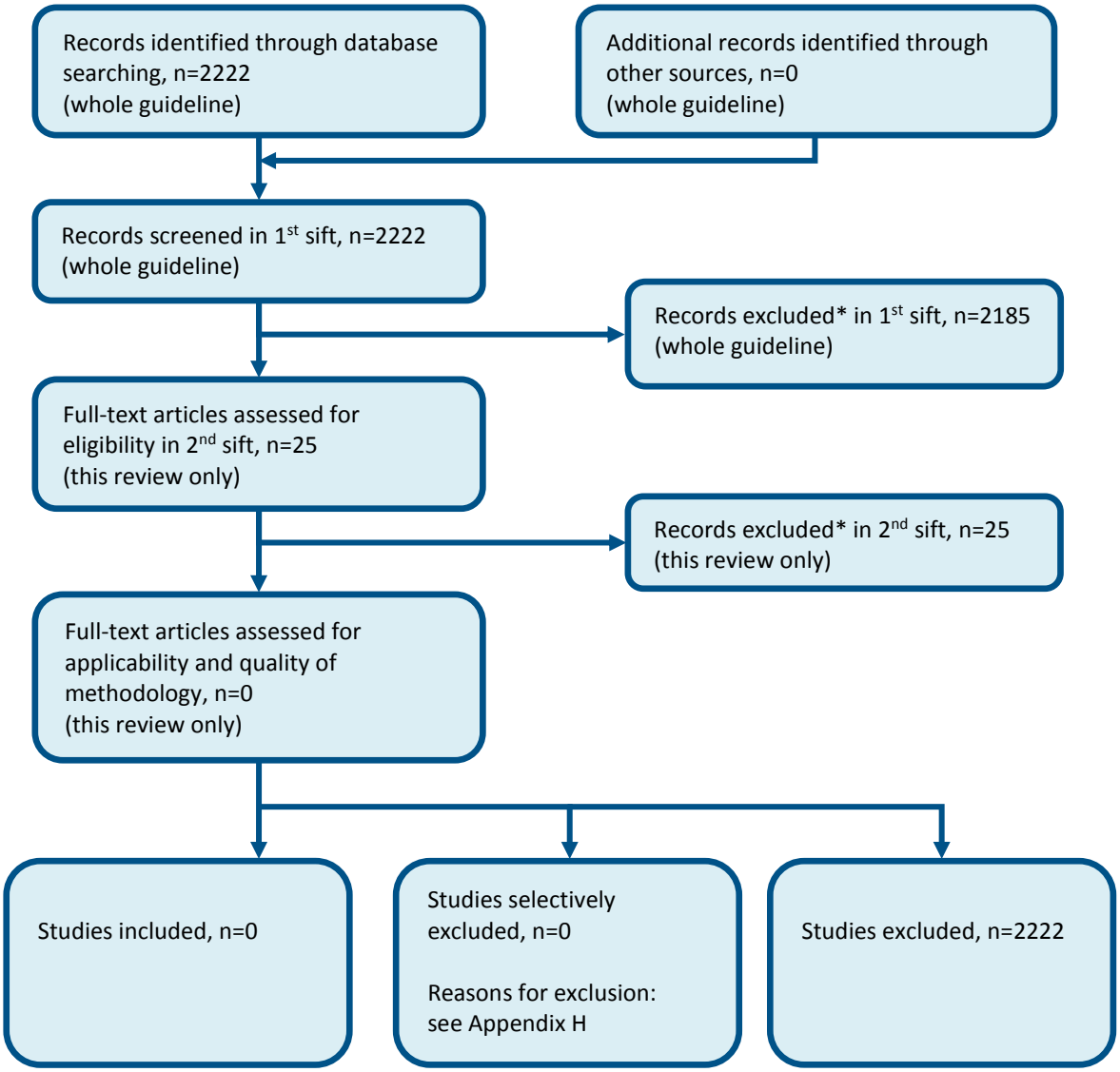
Figure 24: Flow chart of economic article selection for the review of signs and symptoms



* Non-relevant population, intervention, comparison, design or setting; non-English language

E.2 Diagnosis: History of atopic disorders

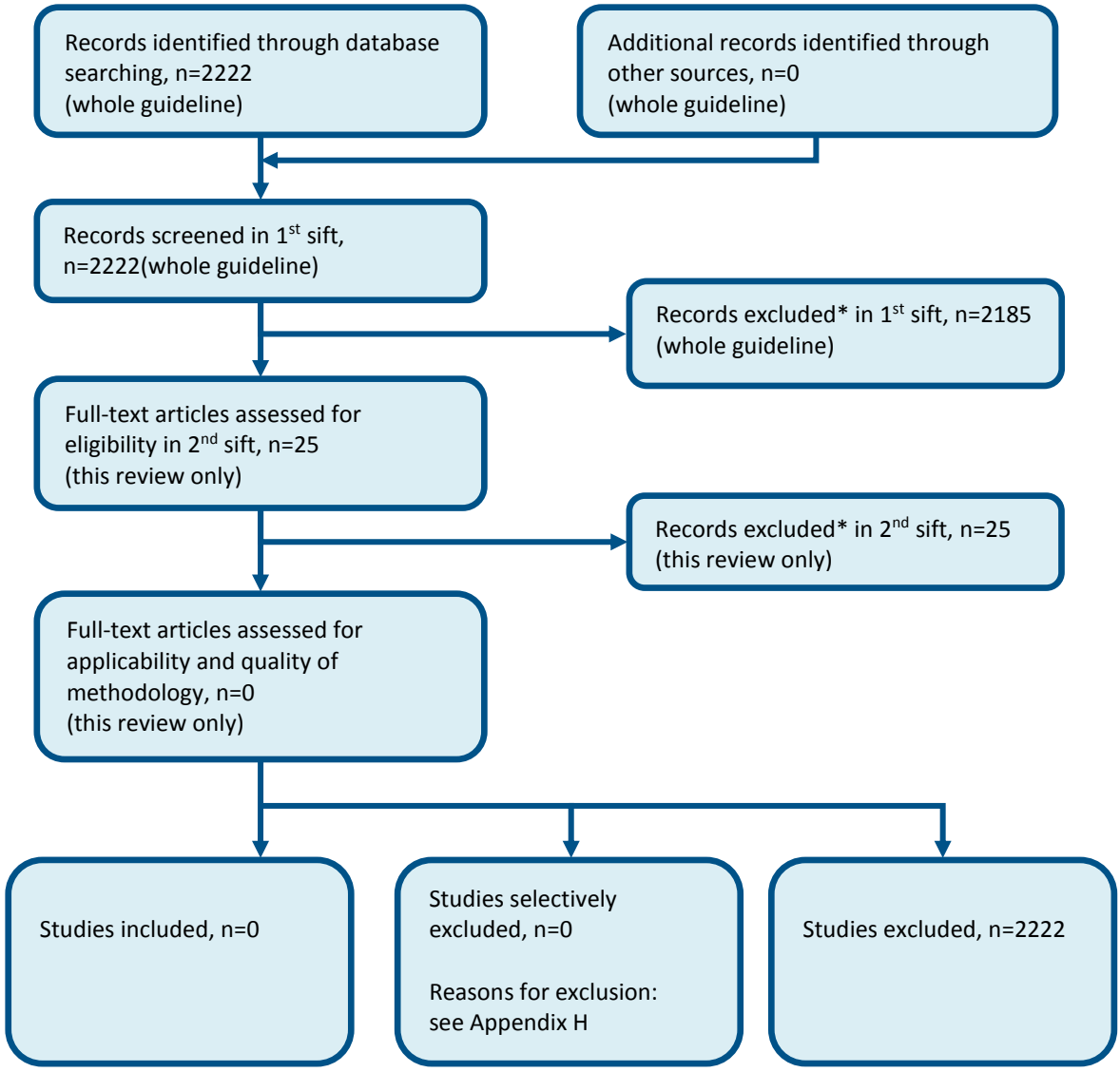
Figure 25: Flow diagram of economic article selection for the review of history of atopic disorders



* Non-relevant population, intervention, comparison, design or setting; non-English language

E.3 Diagnosis: Symptoms after exercise

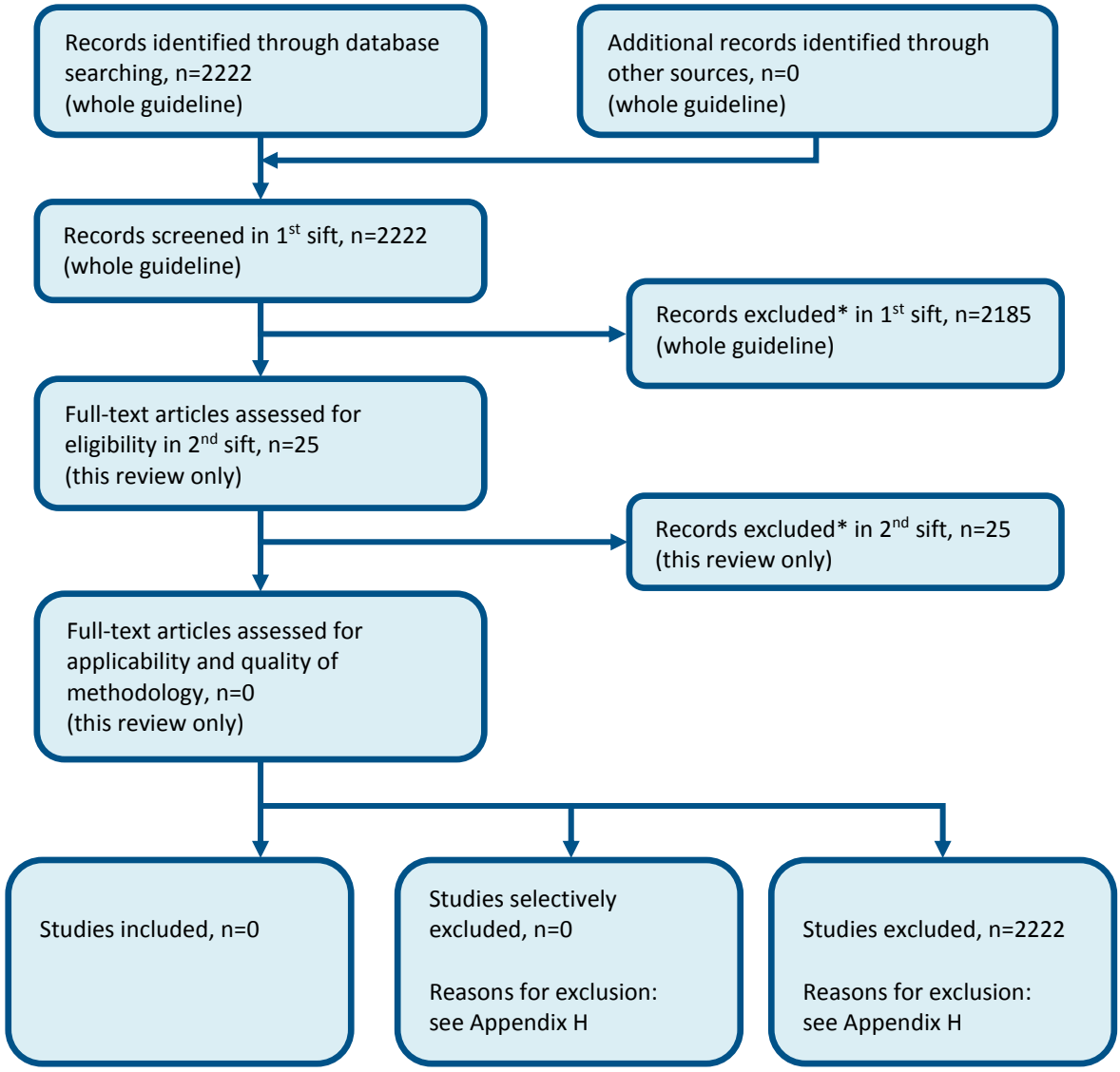
Figure 26: Flow diagram of economic article selection for the review of symptoms in response to exercise



* Non-relevant population, intervention, comparison, design or setting; non-English language

E.4 Diagnosis: Symptoms after using medication

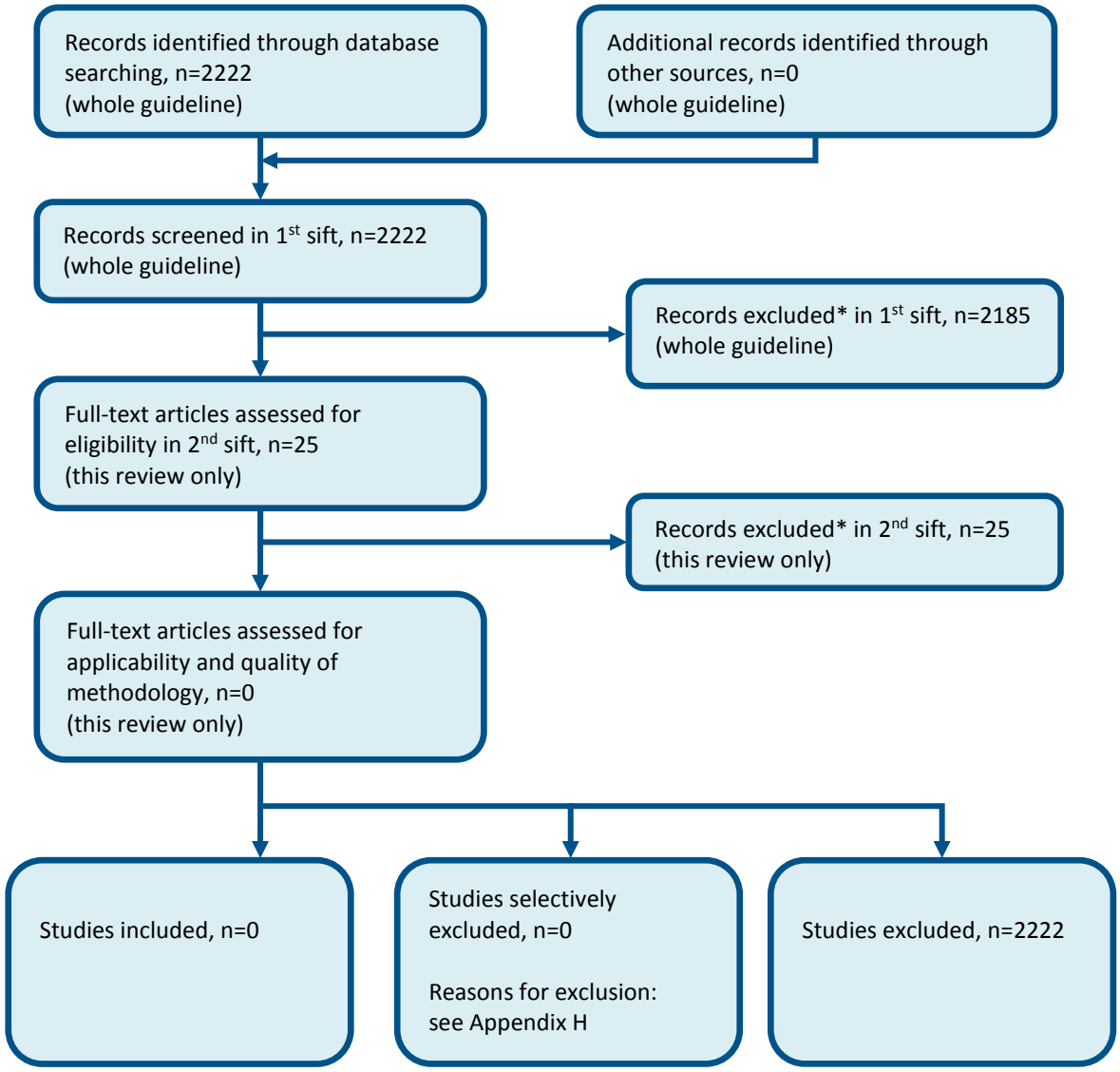
Figure 27: Flow diagram of economic article selection for the review of history of symptoms after using medication



* Non-relevant population, intervention, comparison, design or setting; non-English language

E.5 Diagnosis: Occupational asthma

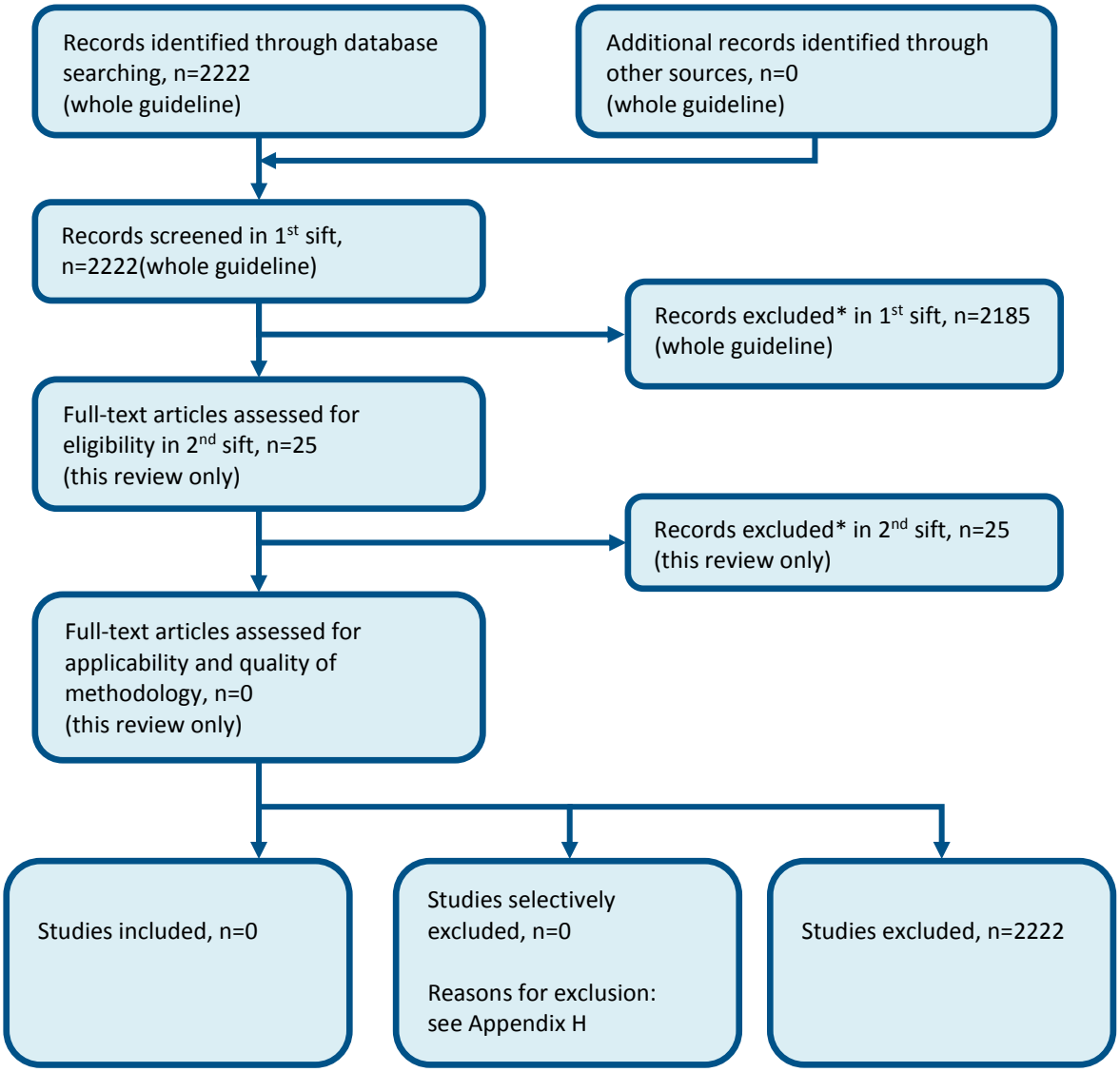
Figure 28: Flow diagram of economic article selection for the review of occupational asthma



* Non-relevant population, intervention, comparison, design or setting; non-English language

E.6 Diagnosis: Spirometry

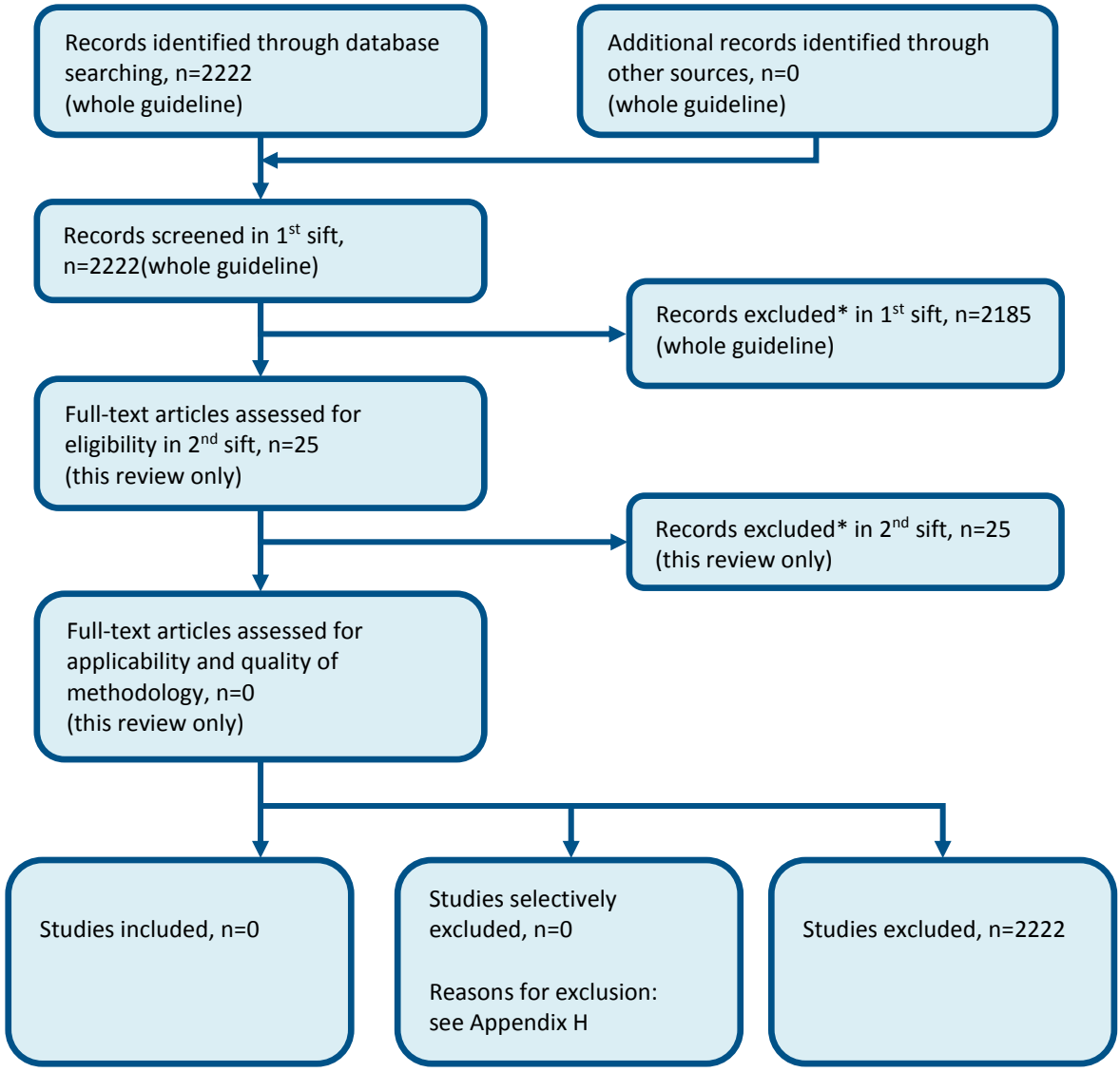
Figure 29: Flow diagram of economic article selection for the review of spirometry



* Non-relevant population, intervention, comparison, design or setting; non-English language

E.7 Diagnosis: Bronchodilator reversibility

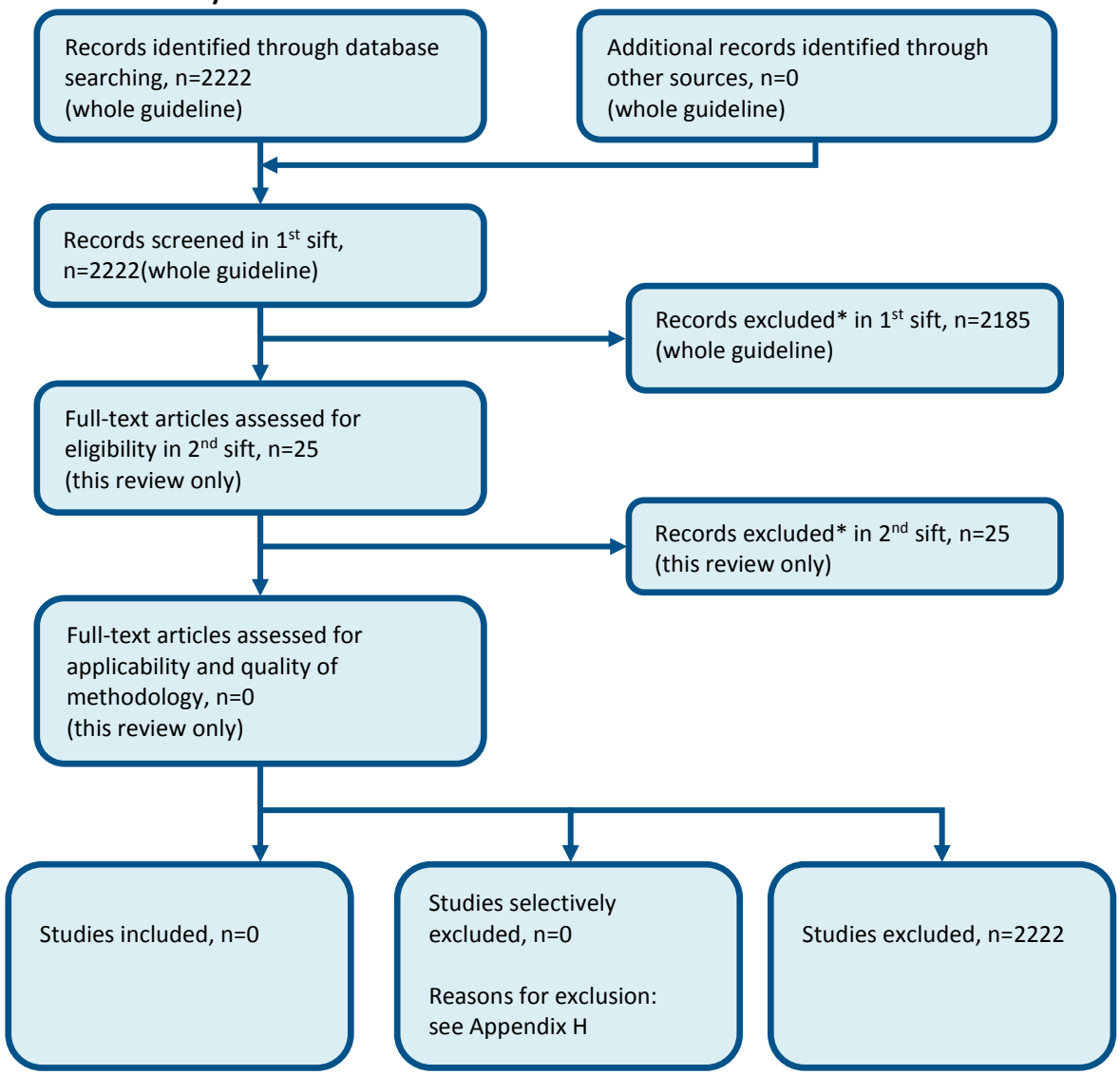
Figure 30: Flow diagram of economic article selection for the review of bronchodilator reversibility



* Non-relevant population, intervention, comparison, design or setting; non-English language

E.8 Diagnosis: PEF variability

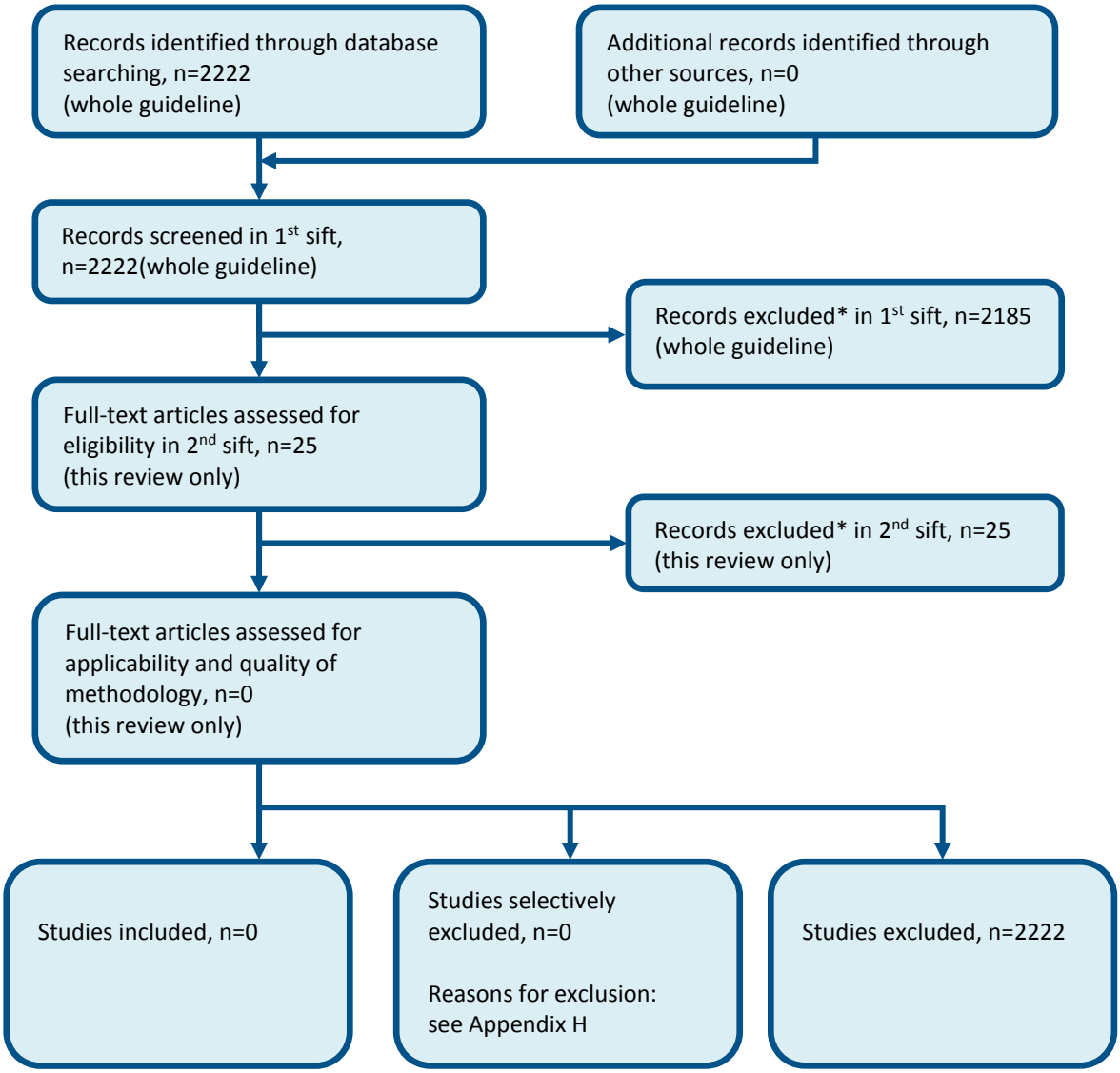
Figure 31: Flow chart of economic article selection for the review of peak expiratory flow variability



* Non-relevant population, intervention, comparison, design or setting; non-English language

E.9 Diagnosis: Skin prick tests

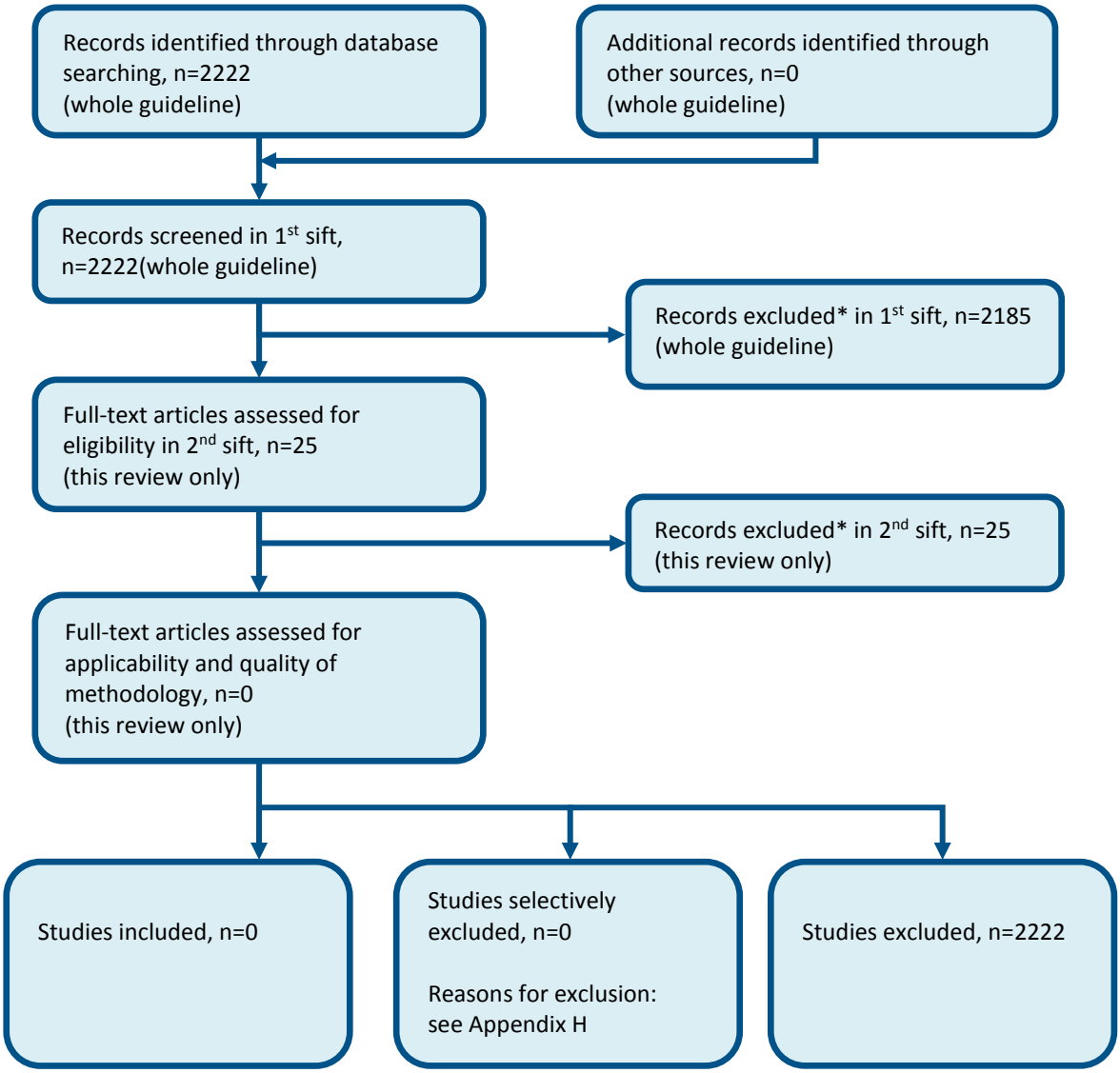
Figure 32: Flow diagram of economic article selection for the review of skin prick tests



* Non-relevant population, intervention, comparison, design or setting; non-English language

E.10 Diagnosis: IgE

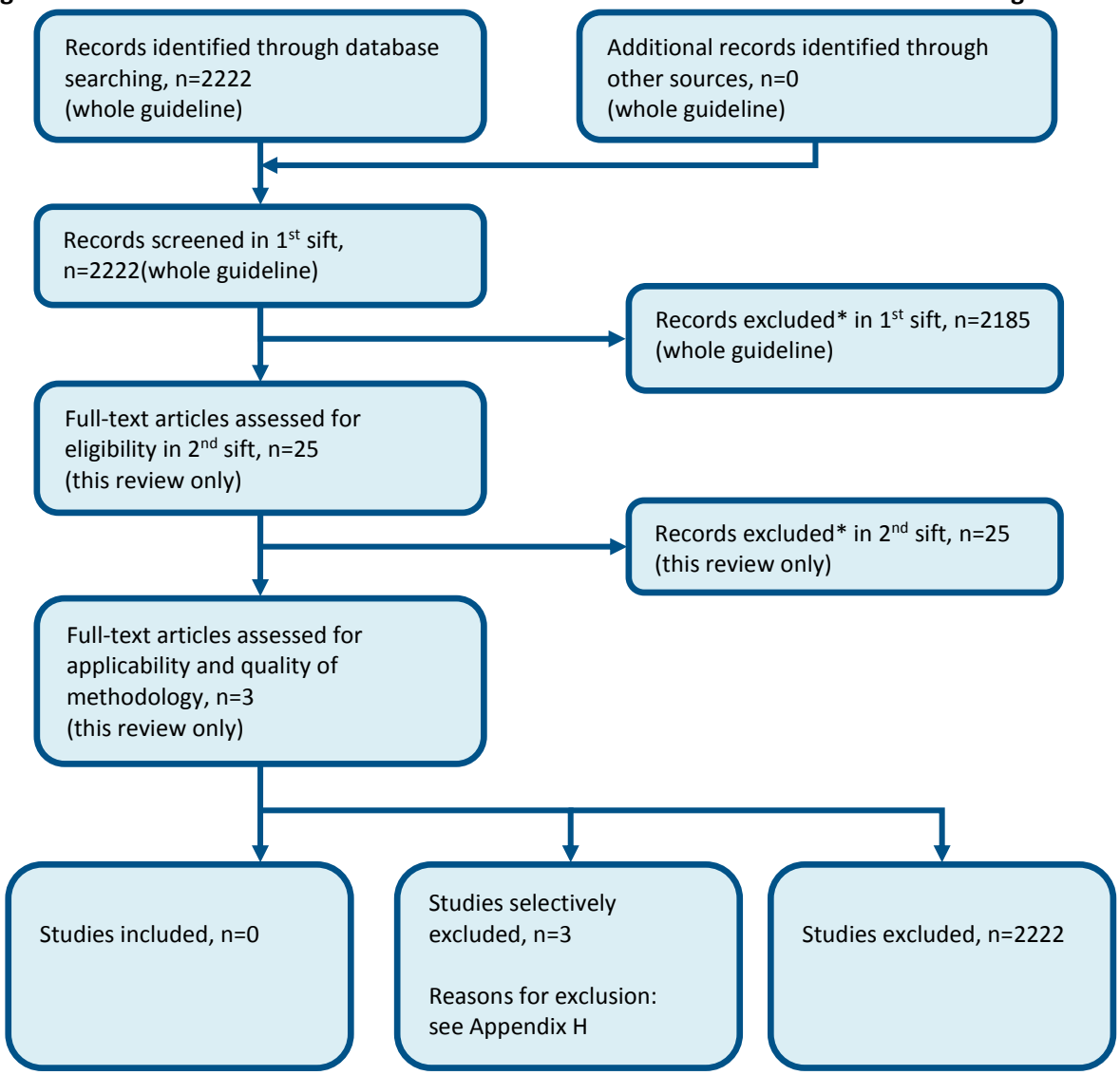
Figure 33: Flow diagram of economic article selection for the review of IgE



* Non-relevant population, intervention, comparison, design or setting; non-English language

E.11 Diagnosis: FeNO

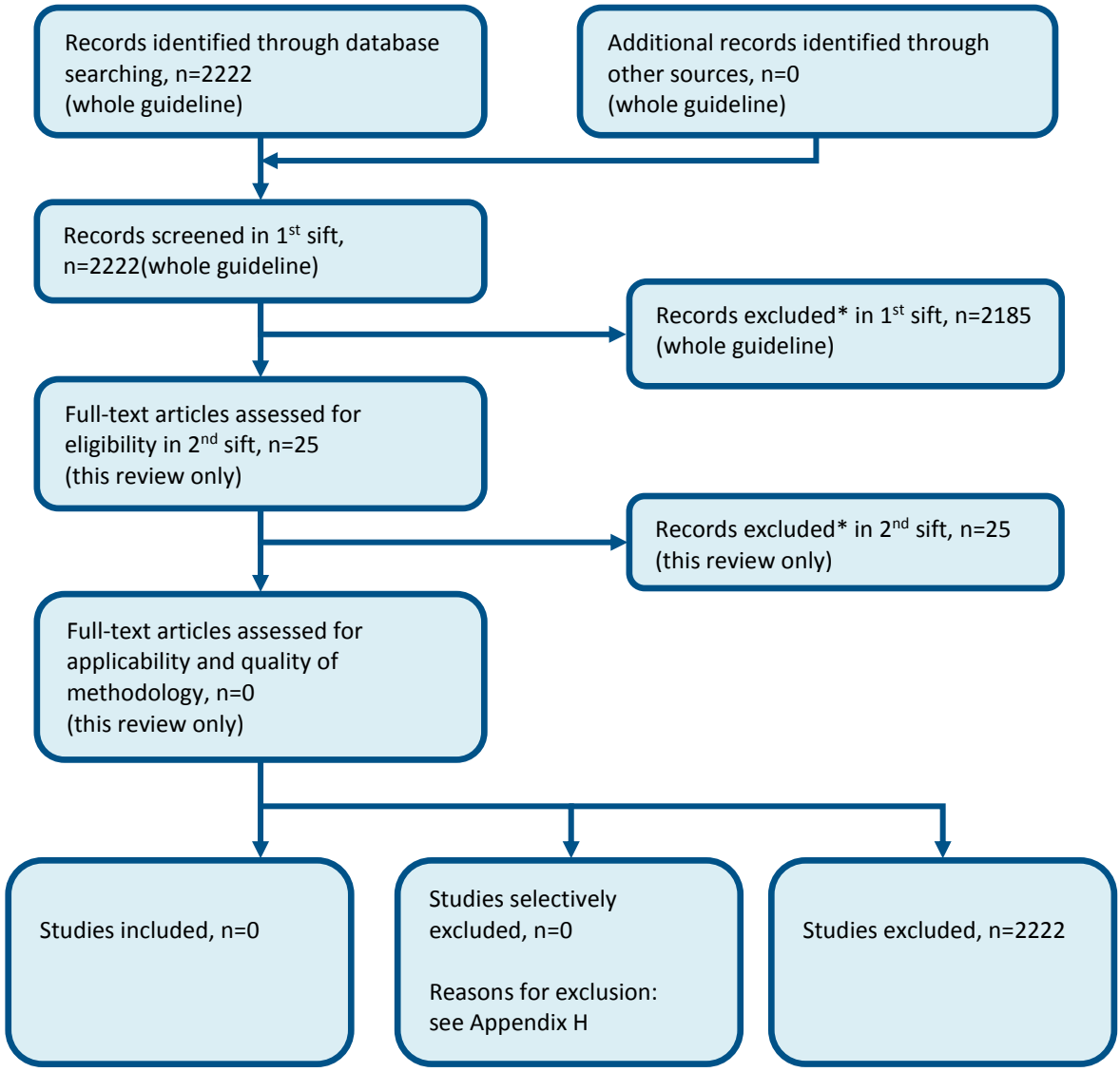
Figure 34: Flow chart of economic article selection for the review of FeNO for asthma diagnosis



* Non-relevant population, intervention, comparison, design or setting; non-English language

E.12 Diagnosis: Eosinophils

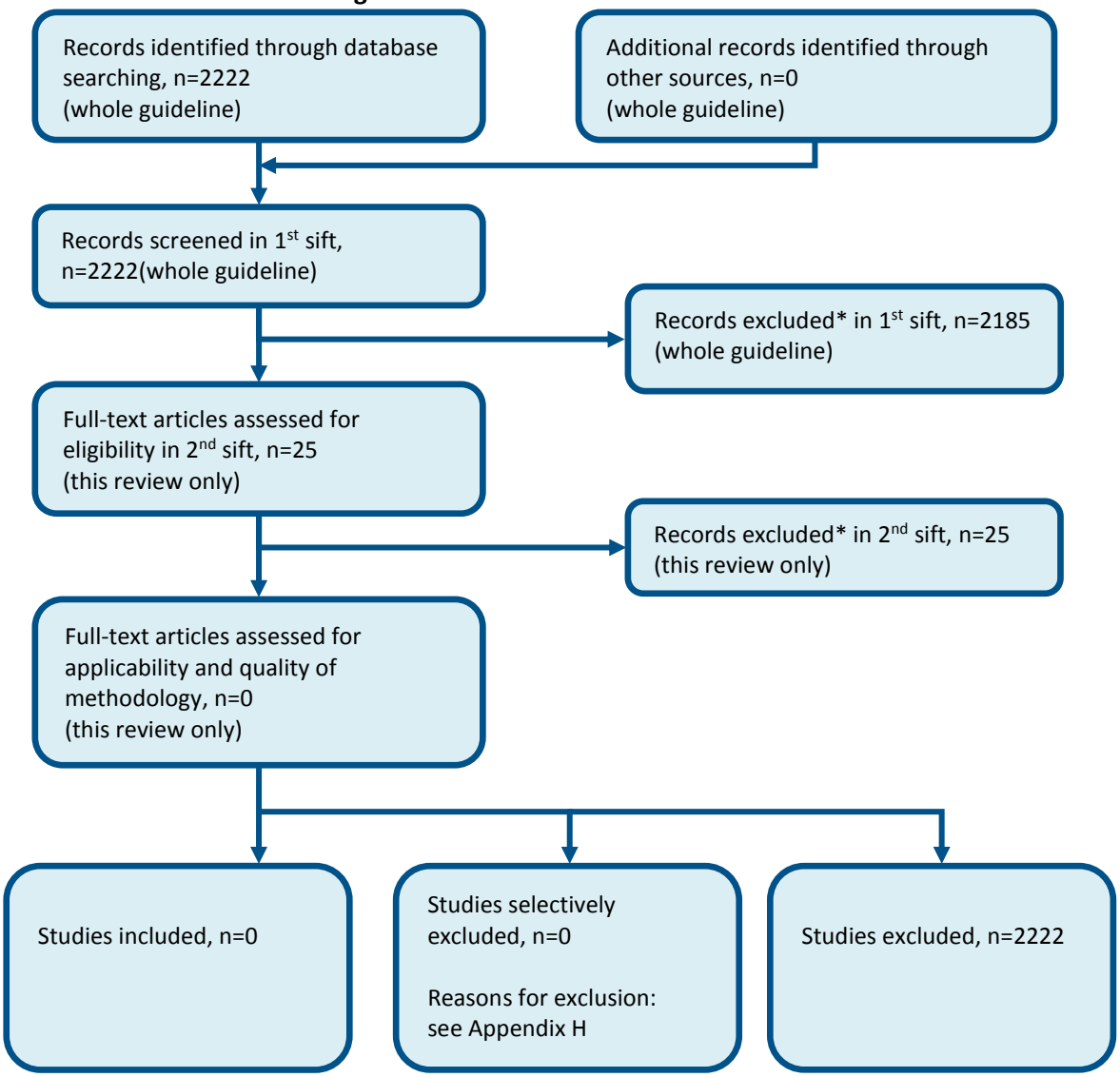
Figure 35: Flow diagram of economic article selection for the review of eosinophils



* Non-relevant population, intervention, comparison, design or setting; non-English language

E.13 Diagnosis: Histamine and methacholine

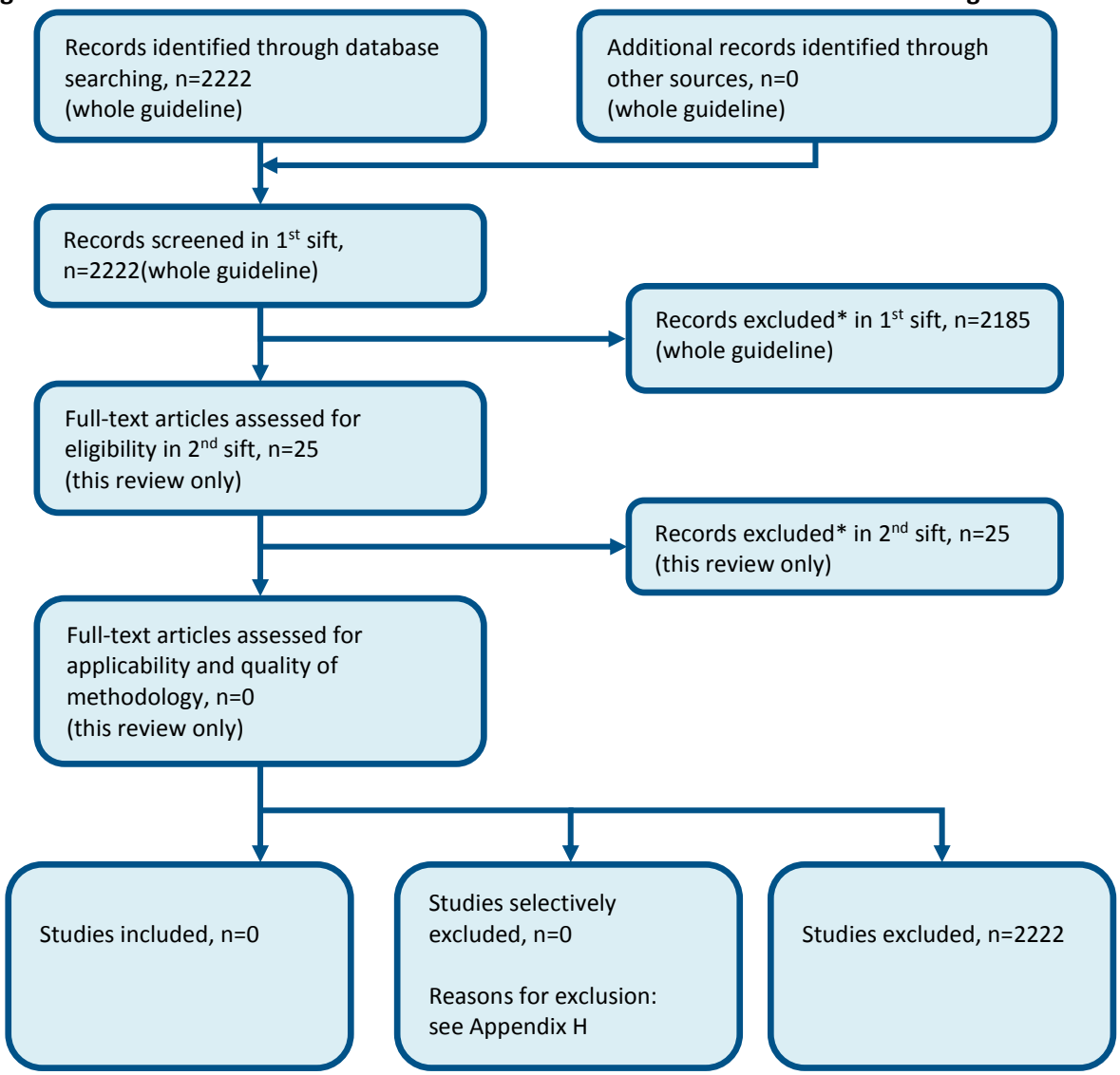
Figure 36: Flow diagram of economic article selection for the review of histamine and methacholine challenge tests



* Non-relevant population, intervention, comparison, design or setting; non-English language

E.14 Diagnosis: Mannitol

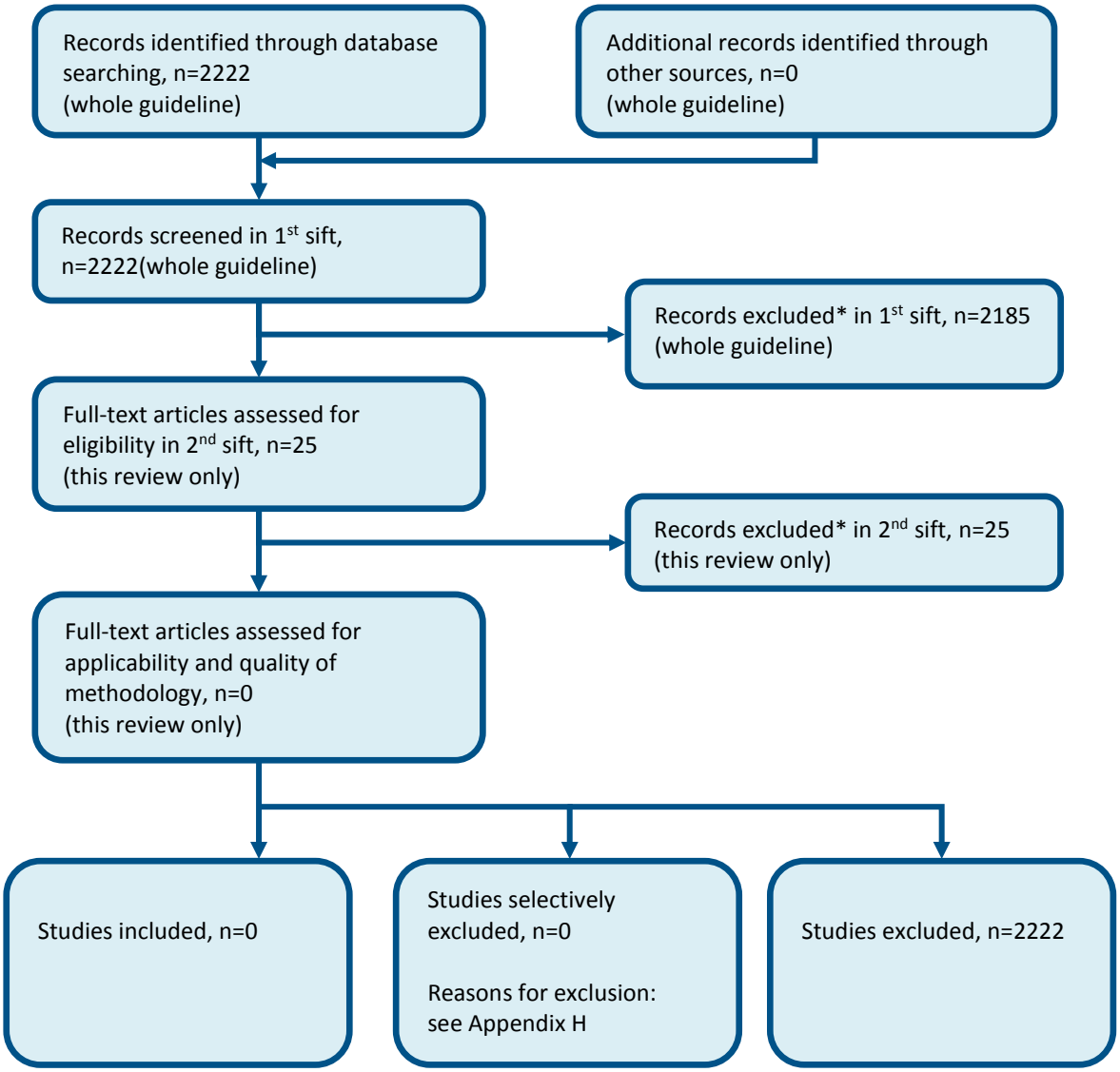
Figure 37: Flow chart of economic article selection for the review of mannitol challenge test



* Non-relevant population, intervention, comparison, design or setting; non-English language

E.15 Diagnosis: Exercise challenge test

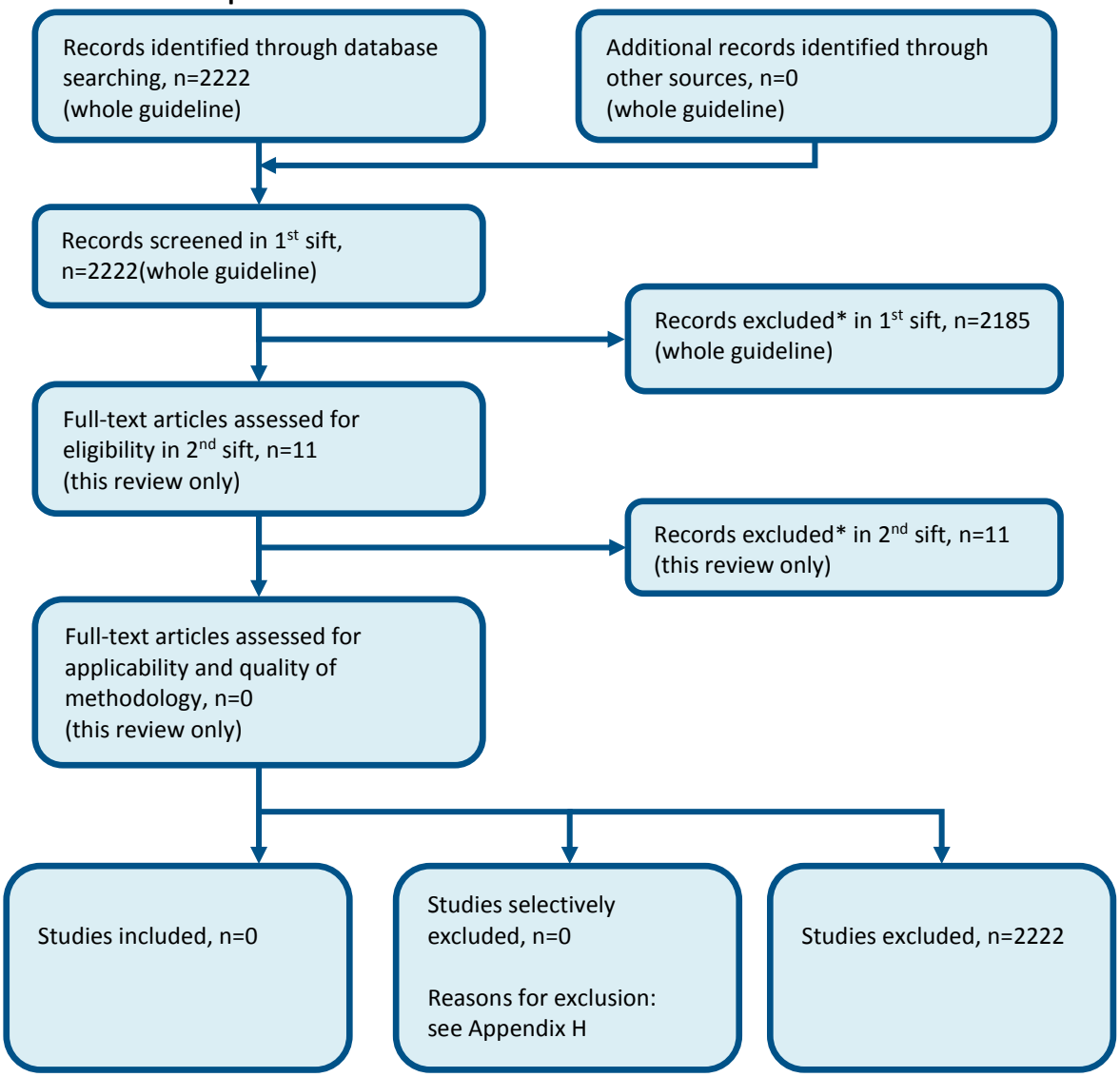
Figure 38: Flow diagram of economic article selection for the review of exercise challenge tests



* Non-relevant population, intervention, comparison, design or setting; non-English language

E.16 Monitoring: Questionnaires

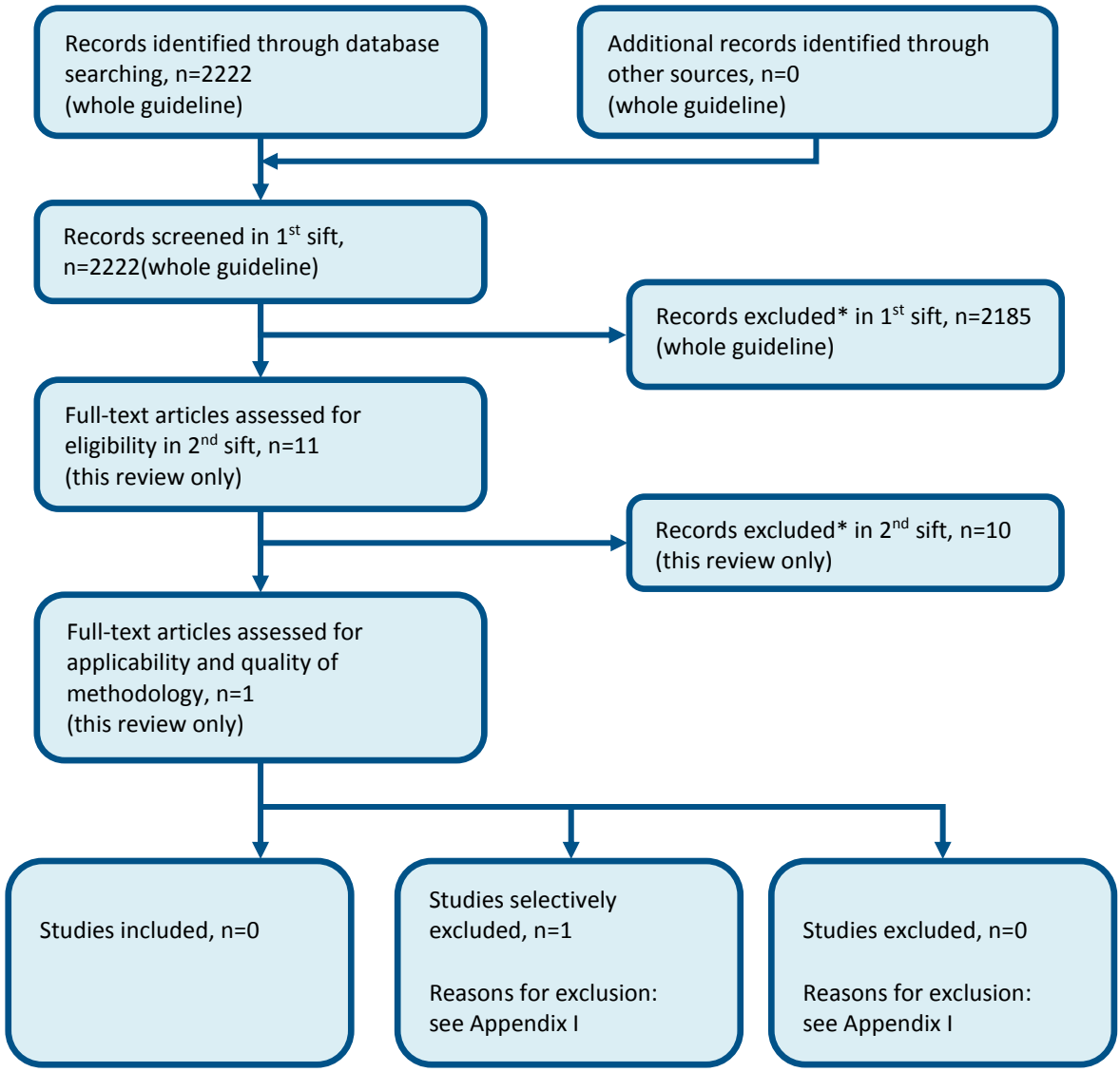
Figure 39: Flow chart of economic article selection for the review of symptom scores/diaries or validated questionnaires to monitor asthma control



* Non-relevant population, intervention, comparison, design or setting; non-English language

E.17 Monitoring: Lung function tests

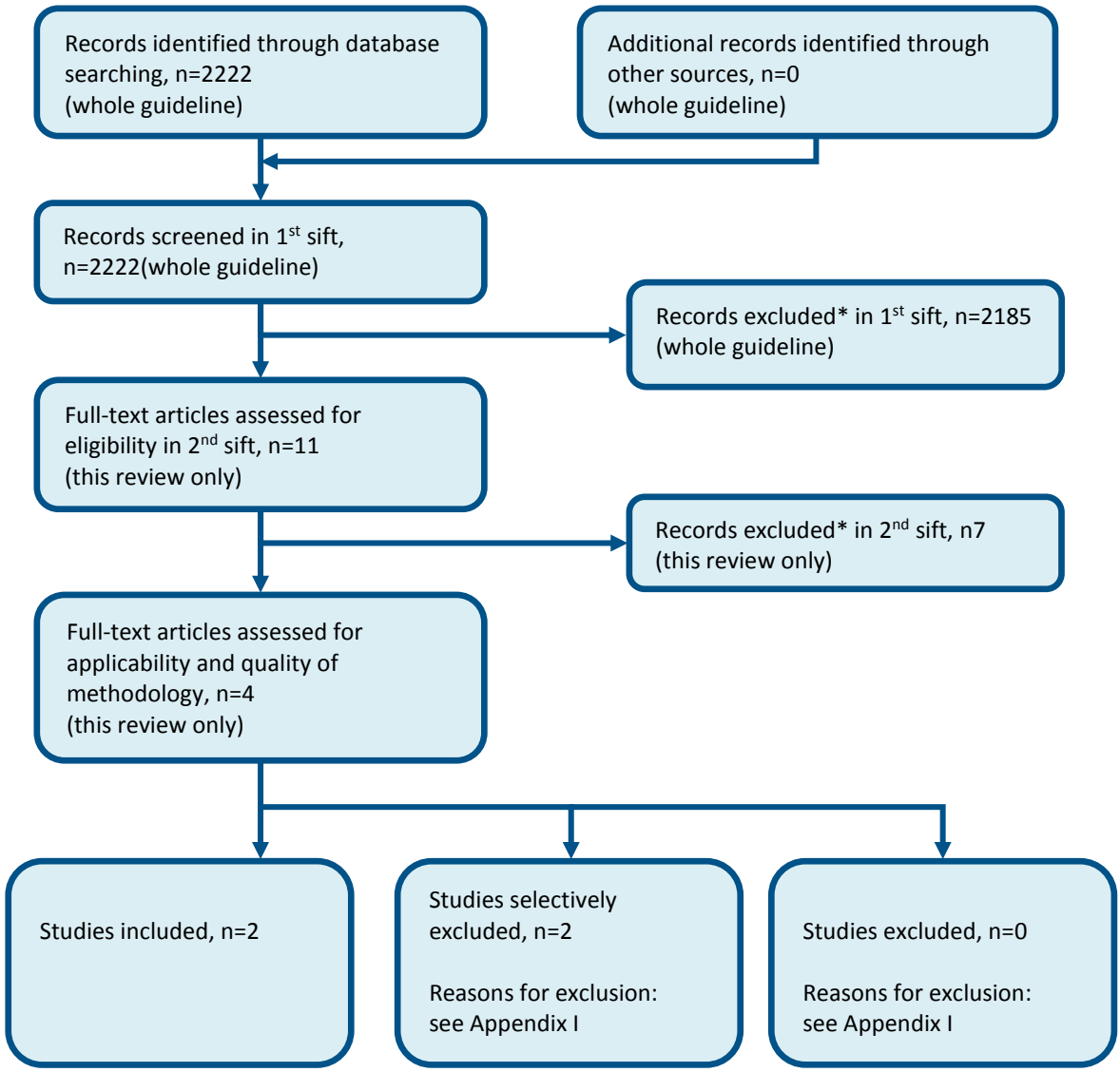
Figure 40: Flow chart of economic article selection for the review of lung function tests to monitor asthma control



* Non-relevant population, intervention, comparison, design or setting; non-English language

E.18 Monitoring: FeNO

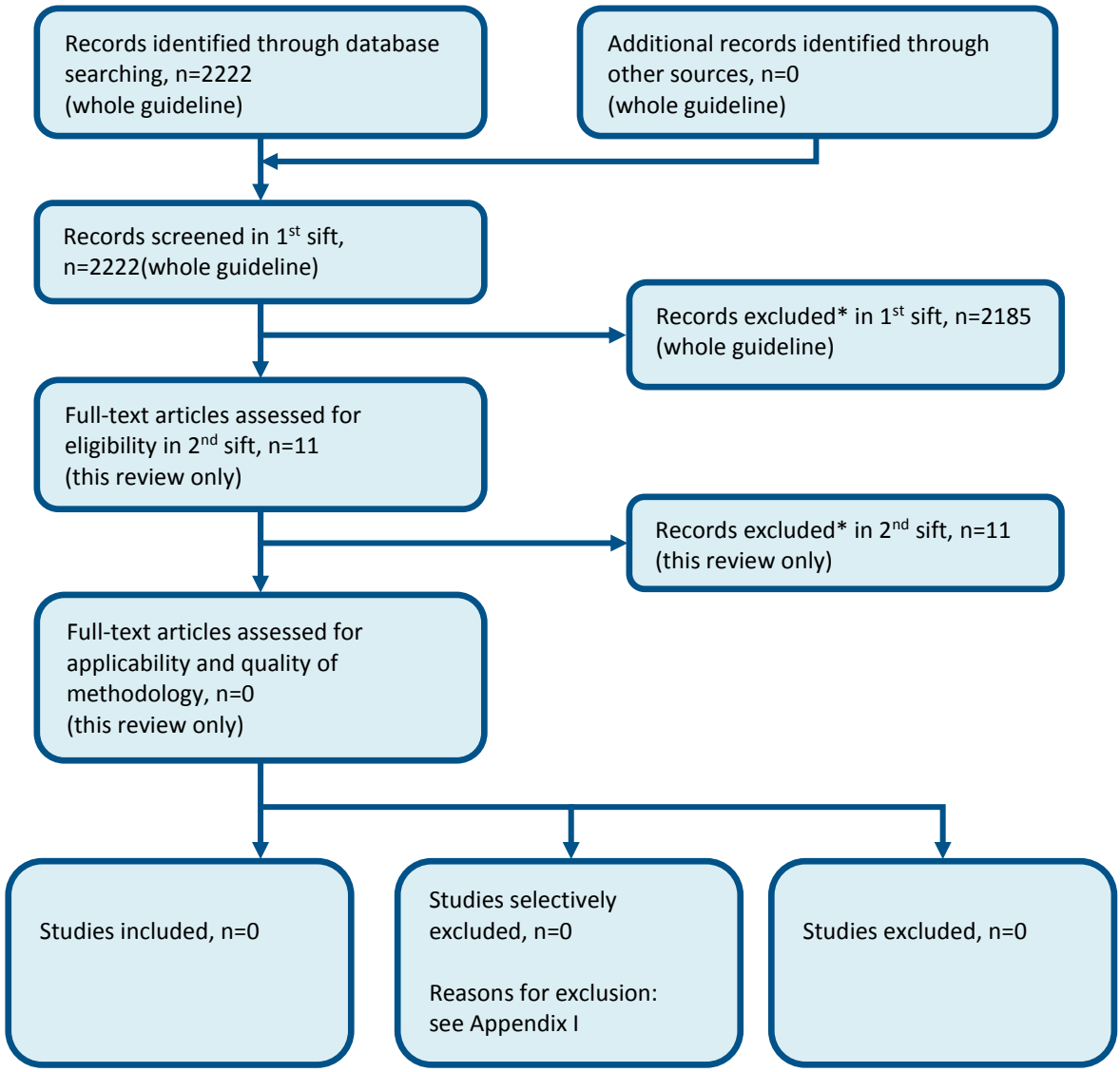
Figure 41: Flow chart of economic article selection for the review of FeNO to monitor asthma control



* Non-relevant population, intervention, comparison, design or setting; non-English language

E.19 Monitoring: Peripheral blood eosinophils

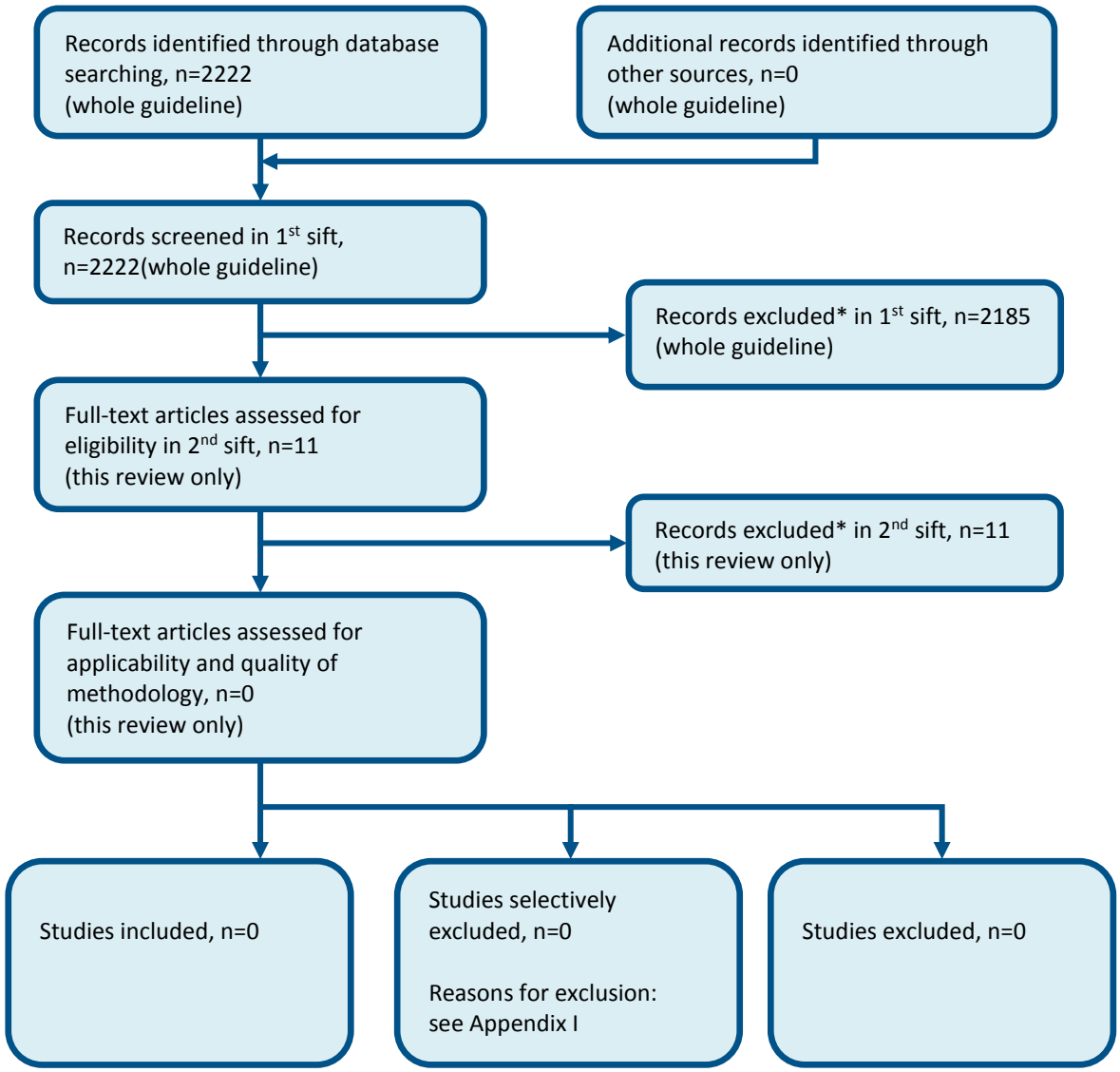
Figure 42: Flow chart of economic article selection for the review of peripheral blood eosinophils to monitor asthma control



* Non-relevant population, intervention, comparison, design or setting; non-English language

E.20 Monitoring: Challenge tests

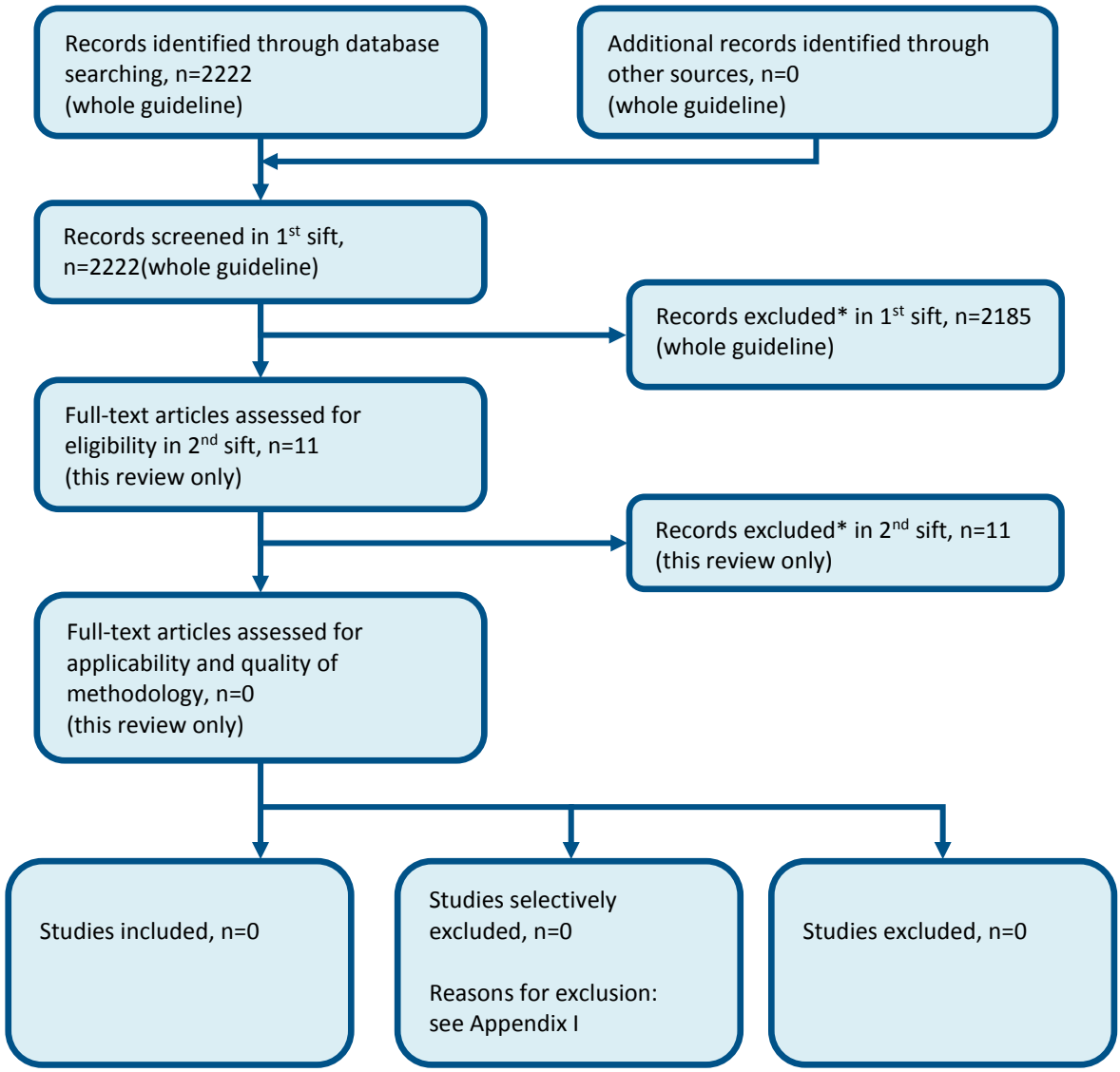
Figure 43: Flow chart of economic article selection for the review of challenge tests to monitor asthma control



* Non-relevant population, intervention, comparison, design or setting; non-English language

E.21 Monitoring: Adherence to treatment

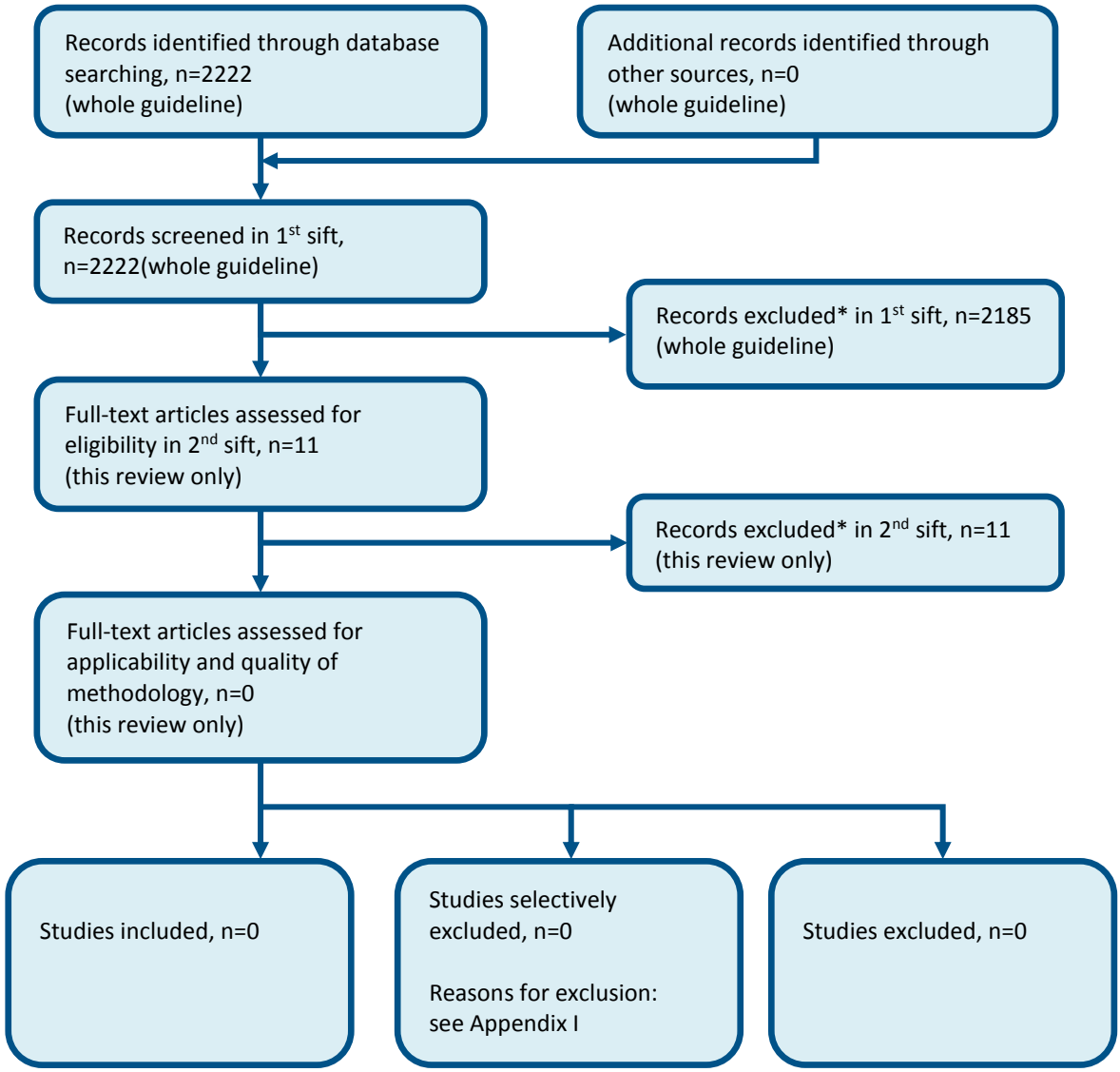
Figure 44: Flow chart of economic article selection for the review of monitoring adherence to treatment



* Non-relevant population, intervention, comparison, design or setting; non-English language

E.22 Monitoring: Inhaler technique

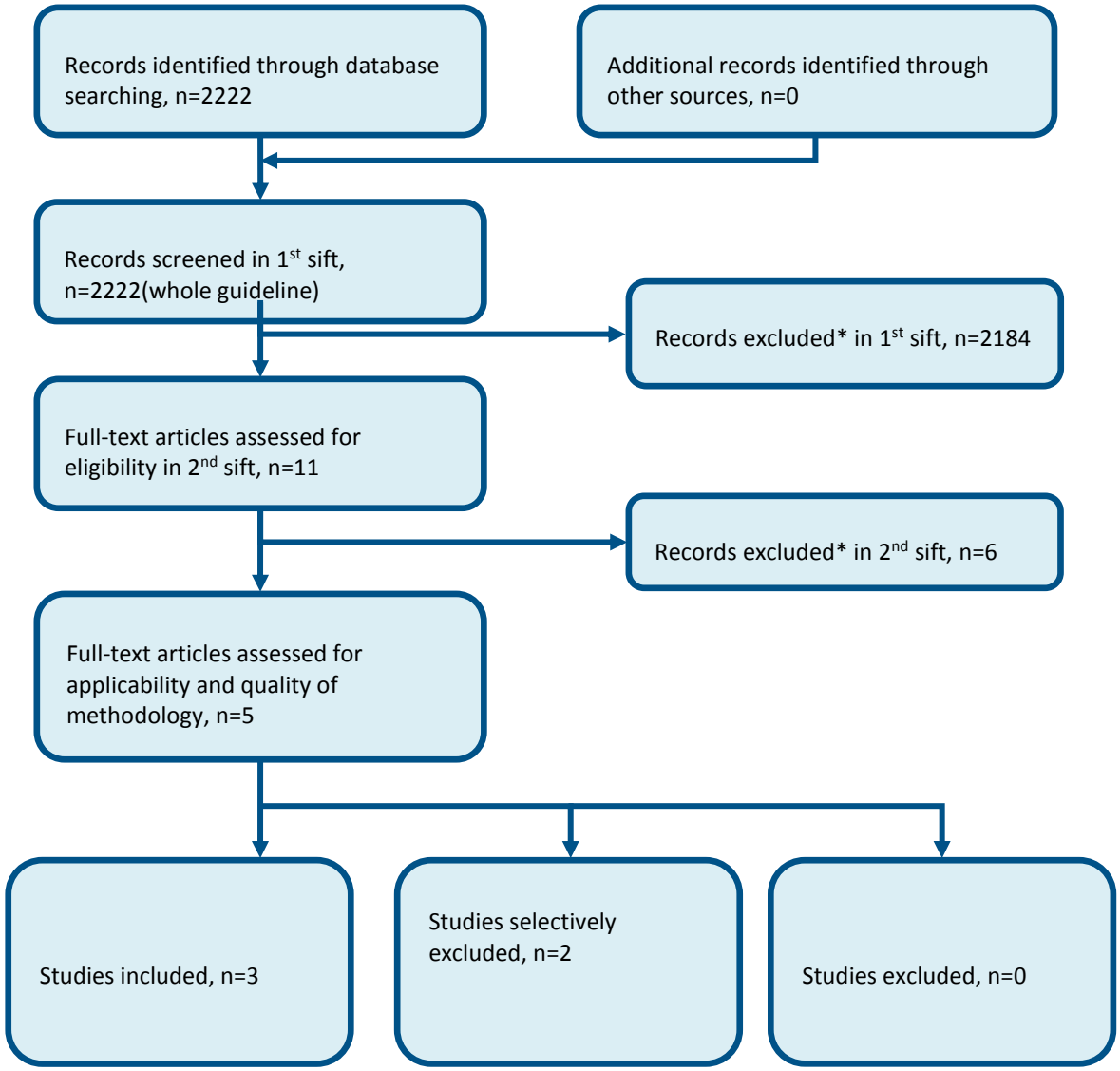
Figure 45: Flow chart of economic article selection for the review of monitoring inhaler technique



* Non-relevant population, intervention, comparison, design or setting; non-English language

E.23 Monitoring: Tele-healthcare

Figure 46: Flow chart of economic article selection for the review of tele-healthcare to monitor asthma control



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix F: Literature search strategies

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Appendix P:	**References**

Search strategies used for the asthma guideline are outlined below and were run in accordance with the methodology in the NICE guidelines manual 2012.[1204] All searches were run up to 1 October 2014 unless otherwise stated. Any studies added to the databases after this date (even those published prior to this date) were not included unless specifically stated in the text. We do not routinely search for electronic, ahead of print or "online early" publications. Where possible searches were limited to retrieve material published in English.

Table 24: Database date parameters

Database	Dates searched
Medline	1946—1 October 2014
Embase	1980 – 1 October 2014 (week 39)
The Cochrane Library	Cochrane Reviews to 2014 Issue 10 of 12 CENTRAL to 2014 Issue 9 of 12 DARE, HTA and NHSEED to 2014 Issue 3 of 4

Searches for the **clinical reviews** were run in Medline (OVID), Embase (OVID) and the Cochrane Library (Wiley).

Searches for **intervention and diagnostic studies** were usually constructed using a PICO format where population (P) terms were combined with Intervention (I) and sometimes Comparison (C) terms. An intervention can be a drug, a procedure or a diagnostic test. Outcomes (O) are rarely used in search strategies for interventions. Search filters were also added to the search where appropriate.

Searches for **prognostic studies** were usually constructed combining population terms with prognostic variable terms and sometimes outcomes. Search filters were added to the search where appropriate.

Searches for the **health economic reviews** were run in Medline (OVID), Embase (OVID), the NHS Economic Evaluations Database (NHS EED), the Health Technology Assessment (HTA) database and the Health Economic Evaluation Database (HEED). Searches in NHS EED and HEED were constructed using population terms only. For Medline and Embase an economic filter (instead of a study type filter) was added to the same clinical search strategy.

F.1 Population search strategies

F.1.1 Standard population

This population was used in all clinical questions except F.3.5 occupational asthma.

Medline and Embase search terms

1.	exp asthma/
2.	asthma*.ti.

3.	or/1-2

Cochrane search terms

#1.	MeSH descriptor: [Asthma] explode all trees
#2.	asthma*:ti
#3.	{or #1-#2}

F.2 Study filter search terms

F.2.1 Systematic review (SR) search terms

Medline search terms

1.	meta-analysis/
2.	meta-analysis as topic/
3.	(meta analy* or metanaly* or metaanaly*).ti,ab.
4.	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9.	cochrane.jw.
10.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
11.	or/1-10

Embase search terms

1.	systematic review/
2.	meta-analysis/
3.	(meta analy* or metanaly* or metaanaly*).ti,ab.
4.	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9.	cochrane.jw.
10.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
11.	or/1-10

F.2.2 Randomised controlled trials (RCTs) search terms

Medline search terms

1.	randomized controlled trial.pt.
2.	controlled clinical trial.pt.
3.	randomi#ed.ab.
4.	placebo.ab.
5.	randomly.ab.
6.	clinical trials as topic.sh.

7.	trial.ti.
8.	or/1-7

Embase search terms

1.	random*.ti,ab.
2.	factorial*.ti,ab.
3.	(crossover* or cross over*).ti,ab.
4.	((doubl* or singl*) adj blind*).ti,ab.
5.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
6.	crossover procedure/
7.	double blind procedure/
8.	single blind procedure/
9.	randomized controlled trial/
10.	or/1-9

F.2.3 Observational studies (OBS) search terms

Medline search terms

1.	epidemiologic studies/
2.	exp case control studies/
3.	exp cohort studies/
4.	cross-sectional studies/
5.	case control.ti,ab.
6.	(cohort adj (study or studies or analys*)).ti,ab.
7.	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
8.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
9.	or/1-8

Embase search terms

1.	clinical study/
2.	exp case control study/
3.	family study/
4.	longitudinal study/
5.	retrospective study/
6.	prospective study/
7.	cross-sectional study/
8.	cohort analysis/
9.	follow-up/
10.	cohort*.ti,ab.
11.	9 and 10
12.	case control.ti,ab.
13.	(cohort adj (study or studies or analys*)).ti,ab.
14.	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
15.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.

16.	or/1-8,11-15

Cochrane search terms

#1.	case control:ti,ab,kw
#2.	(cohort near/2 (study or studies or analys*)):ti,ab,kw
#3.	((follow up or observational or uncontrolled or non randomi?ed or nonrandomi?ed or epidemiologic*) near/2 (study or studies)):ti,ab,kw
#4.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)):ti,ab,kw
#5.	{or #1-#4}

F.2.4 Diagnostic test accuracy studies (DIAG1) search terms

Medline search terms

1.	exp "sensitivity and specificity"/
2.	(sensitivity or specificity).ti,ab.
3.	((pre test or pretest or post test) adj probability).ti,ab.
4.	(predictive value* or PPV or NPV).ti,ab.
5.	likelihood ratio*.ti,ab.
6.	likelihood function/
7.	(ROC curve* or AUC).ti,ab.
8.	(diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
9.	gold standard.ab.
10.	or/1-9

Embase search terms

1.	exp "sensitivity and specificity"/
2.	(sensitivity or specificity).ti,ab.
3.	((pre test or pretest or post test) adj probability).ti,ab.
4.	(predictive value* or PPV or NPV).ti,ab.
5.	likelihood ratio*.ti,ab.
6.	(ROC curve* or AUC).ti,ab.
7.	(diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
8.	diagnostic accuracy/
9.	diagnostic test accuracy study/
10.	gold standard.ab.
11.	or/1-10

Cochrane search terms

#1.	diagnos*:ti,ab,kw
#2.	(sensitivity or specificity):ti,ab,kw
#3.	((pre test or pretest or post test) near probability):ti,ab,kw
#4.	(predictive value* or PPV or NPV):ti,ab,kw
#5.	likelihood ratio*:ti,ab,kw
#6.	(ROC or AUC):ti,ab,kw
#7.	gold standard:ti,ab,kw

#8.	Any MeSH descriptor with qualifier(s): [Diagnosis - DI]
#9.	{or #1-#8}

F.2.5 Diagnostic studies (DIAG2) search terms

The following terms were added to the diagnostic test accuracy search terms in F.2.4 to create a more sensitive search in Medline and Embase only.

Medline and Embase search terms

1.	sensitiv*.mp.
2.	diagnos*.mp.
3.	di.fs.
4.	or/1-3

F.2.6 Prognostic studies (PROG) search terms

Medline search terms

1.	predict.ti.
2.	(validat* or rule*).ti,ab.
3.	(predict* and (outcome* or risk* or model*)).ti,ab.
4.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
5.	decision*.ti,ab. and Logistic models/
6.	(decision* and (model* or clinical*)).ti,ab.
7.	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
8.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
9.	ROC curve/
10.	or/1-9

Embase search terms

1.	predict.ti.
2.	(validat* or rule*).ti,ab.
3.	(predict* and (outcome* or risk* or model*)).ti,ab.
4.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
5.	decision*.ti,ab. and statistical model/
6.	(decision* and (model* or clinical*)).ti,ab.
7.	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
8.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or auc or calibration or indices or algorithm or multivariable).ti,ab.
9.	receiver operating characteristic/
10.	or/1-9
11.	predict.ti.

Cochrane search terms

#1.	predict:ti,ab,kw

#2.	(validat* or rule*):ti,ab,kw
#3.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (model* or decision* or identif* or prognos*)):ti,ab,kw
#4.	(decision* and (model* or clinical*)):ti,ab,kw
#5.	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)):ti,ab,kw
#6.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or calibration or indices or algorithm or multivariable):ti,ab,kw
#7.	{or #1-#6}

F.2.7 Validation (VAL) studies search terms

Medline search terms

1.	validation studies/
2.	reproducibility of results/
3.	(valid* or reliab*).ti,ab.
4.	observer variation/
5.	((inter* or intra* or observer* or rater*) adj3 (bias* or variation* or agree* or concordan*)).ti,ab.
6.	or/1-5

Embase search terms

1.	(valid* or reliab*).ti,ab.
2.	((inter* or intra* or observer* or rater*) adj3 (bias* or variation* or agree* or concordan*)).ti,ab.
3.	validation study/
4.	exp reliability/
5.	exp reproducibility/
6.	exp observer variation/
7.	or/1-6

F.2.8 Health economics (HE) search terms

Medline search terms

1.	economics/
2.	value of life/
3.	exp "costs and cost analysis"/
4.	exp economics, hospital/
5.	exp economics, medical/
6.	economics, nursing/
7.	economics, pharmaceutical/
8.	exp "fees and charges"/
9.	exp budgets/
10.	budget*.ti,ab.
11.	cost*.ti.
12.	(economic* or pharmaco?economic*).ti.
13.	(price* or pricing*).ti,ab.
14.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.

15.	(financ* or fee or fees).ti,ab.
16.	(value adj2 (money or monetary)).ti,ab.
17.	or/1-16

Embase search terms

1.	health economics/
2.	exp economic evaluation/
3.	exp health care cost/
4.	exp fee/
5.	budget/
6.	funding/
7.	budget*.ti,ab.
8.	cost*.ti.
9.	(economic* or pharmaco?economic*).ti.
10.	(price* or pricing*).ti,ab.
11.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
12.	(financ* or fee or fees).ti,ab.
13.	(value adj2 (money or monetary)).ti,ab.
14.	or/1-13

F.2.9 Quality of life (QOL) search terms

Medline search terms

1.	(euroqol* or eq5d* or eq 5d*).ti,ab.

Embase search terms

1.	(euroqol* or eq5d* or eq 5d*).ti,ab.

F.2.10 Excluded study designs and publication types

The following study designs and publication types were removed from retrieved results using the NOT operator.

Medline search terms

1.	letter/
2.	editorial/
3.	news/
4.	exp historical article/
5.	anecdotes as topic/
6.	comment/
7.	case report/
8.	(letter or comment*).ti.
9.	or/1-8
10.	randomized controlled trial/ or random*.ti,ab.
11.	9 not 10
12.	animals/ not humans/
13.	exp animals, laboratory/
14.	exp animal experimentation/

15.	exp models, animal/
16.	exp rodentia/
17.	(rat or rats or mouse or mice).ti.
18.	or/11-17

Embase search terms

1.	letter.pt. or letter/
2.	note.pt.
3.	editorial.pt.
4.	case report/ or case study/
5.	(letter or comment*).ti.
6.	or/1-5
7.	randomized controlled trial/ or random*.ti,ab.
8.	6 not 7
9.	animal/ not human/
10.	nonhuman/
11.	exp animal experiment/
12.	exp experimental animal/
13.	animal model/
14.	exp rodent/
15.	(rat or rats or mouse or mice).ti.
16.	or/8-15

F.3 Searches for specific questions

F.3.1 Signs and Symptoms

6. In people under investigation for asthma, what is the diagnostic accuracy of each of the following signs and symptoms?
   - wheezing
   - cough
   - breathlessness
   - nocturnal symptoms
   - diurnal and seasonal variations.

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Signs and symptoms of asthma as listed in the question	n/a	The following filters were used in all databases: DIAG1, OBS, PROG	See Table 24 English only Exclusion filter applied in Medline and Embase

Medline search terms

1.	*respiratory sounds/

2.	*cough/
3.	*dyspnea/
4.	exp *periodicity/
5.	(wheez* or rhonchi or cough* or breathless* or dyspn?ea).ti,ab.
6.	((difficult* or labo?r* or short*) adj2 breath*).ti,ab.
7.	((24h* or 24 hour* or 24 hr*) adj2 (rhythm* or varia* or change* or pattern* or symptom* or sign or signs)).ti,ab.
8.	((season* or diurnal or circadian or nyctohemeral or night* or nocturnal) adj3 (wheez* or rhonchi or cough* or breathless* or dyspn?ea or symptom or symptoms or sign or signs or asthma*)).ti,ab.
9.	or/1-8

Embase search terms

1.	*wheezing/
2.	*irritative coughing/
3.	*chronic cough/
4.	*coughing/
5.	*dyspnea/
6.	*abnormal respiratory sound/
7.	*seasonal variation/
8.	exp *periodicity/
9.	((difficult* or labo?r* or short*) adj2 breath*).ti,ab.
10.	((24h* or 24 hour* or 24 hr*) adj2 (rhythm* or varia* or change* or pattern* or symptom* or sign or signs)).ti,ab.
11.	((season* or diurnal or circadian or nyctohemeral or night* or nocturnal) adj3 (wheez* or rhonchi or cough* or breathless* or dyspn?ea or symptom or symptoms or sign or signs or asthma*)).ti,ab.
12.	(wheez* or rhonchi or cough* or breathless* or dyspn?ea).ti,ab.
13.	or/1-12

Cochrane search terms

#1.	MeSH descriptor: [Respiratory Sounds] this term only
#2.	MeSH descriptor: [Cough] this term only
#3.	MeSH descriptor: [Dyspnea] this term only
#4.	MeSH descriptor: [Periodicity] explode all trees
#5.	(wheez* or rhonchi or cough* or breathless* or dyspn?ea):ti,ab,kw
#6.	((difficult* or labo?r* or short*) near/2 breath*):ti,ab,kw
#7.	((24h* or 24 hour* or 24 hr*) near/2 (rhythm* or varia* or change* or pattern* or symptom* or sign or signs)):ti,ab,kw
#8.	((season* or diurnal or circadian or nyctohemeral or night* or nocturnal) near/3 (wheez* or rhonchi or cough* or breathless* or dyspn?ea or symptom or symptoms or sign or signs or asthma*)):ti,ab,kw
#9.	{or #1-#8}

F.3.2 Personal/family history of atopic disorders

7. In people under investigation for asthma, what is the diagnostic accuracy of taking a personal/family history of atopic disorders?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Personal/family history of atopic disorders	n/a	The following filters were used in all databases: DIAG1, PROG	See Table 24 English only Exclusion filter applied in Medline and Embase

Medline search terms

1.	medical history taking/
2.	(histories or history).ti,ab.
3.	exp questionnaires/
4.	question?aire*.ti,ab.
5.	or/1-4
6.	(atopic or atopy).ti,ab.
7.	(histor* adj2 (hypersensitiv* or allerg*)).ti,ab.
8.	((family or familial or relative? or kin or kinship or brother? or sister? or mother? or father? or son? or daughter? or parent?) adj3 (hypersensitiv* or allerg*)).ti,ab.
9.	rhinitis, allergic, seasonal/
10.	rhinitis, allergic, perennial/
11.	dermatitis, atopic/
12.	exp food hypersensitivity/
13.	((hypersensitiv* or allerg*) adj2 asthma*).ab.
14.	(hay fever or hayfever or pollinosis).ti,ab.
15.	(pollen* adj2 (sensitiv* or hypersensitiv* or allerg*)).ti,ab.
16.	allergic rhinitis.ti,ab.
17.	eczema.ti,ab.
18.	((food* or wheat or nut* or peanut* or milk or dairy or egg* or soy* or sesame or seed* or pecan* or pistachio* or walnut* or coconut* or fish or shellfish or seafood* or cereal* or gluten* or barley or corn* or maize) adj2 (sensitiv* or hypersensitiv* or allerg*)).ti,ab.
19.	or/6-18
20.	5 and 19

Embase search terms

1.	exp *anamnesis/
2.	(histories or history).ti,ab.
3.	exp *questionnaire/
4.	question?aire*.ti,ab.
5.	or/1-4
6.	(atopic or atopy).ti,ab.
7.	(histor* adj2 (hypersensitiv* or allerg*)).ti,ab.
8.	((family or familial or relative? or kin or kinship or brother? or sister? or mother? or father? or son? or daughter? or parent?) adj3 (hypersensitiv* or allerg*)).ti,ab.
9.	((hypersensitiv* or allerg*) adj2 asthma*).ab.
10.	(hay fever or hayfever or pollinosis).ti,ab.

11.	(pollen* adj2 (sensitiv* or hypersensitiv* or allerg*)).ti,ab.
12.	allergic rhinitis.ti,ab.
13.	eczema.ti,ab.
14.	((food* or wheat or nut* or peanut* or milk or dairy or egg* or soy* or sesame or seed* or pecan* or pistachio* or walnut* or coconut* or fish or shellfish or seafood* or cereal* or gluten* or barley or corn* or maize) adj2 (sensitiv* or hypersensitiv* or allerg*)).ti,ab.
15.	*atopic dermatitis/
16.	*atopy/
17.	exp *allergic rhinitis/
18.	exp *food allergy/
19.	or/6-18
20.	5 and 19

Cochrane search terms

#1.	(histories or history or question*):ti,ab,kw
#2.	(atopic or atopy):ti,ab,kw
#3.	(histor* near/2 (hypersensitiv* or allerg*)):ti,ab,kw
#4.	((family or familial or relative? or kin or kinship or brother? or sister? or mother? or father? or son? or daughter? or parent?) near/3 (hypersensitiv* or allerg*)):ti,ab,kw
#5.	((hypersensitiv* or allerg*) near/2 asthma*):ti,ab,kw
#6.	(hay fever or hayfever or pollinosis):ti,ab,kw
#7.	(pollen* near/2 (sensitiv* or hypersensitiv* or allerg*)):ti,ab,kw
#8.	allergic rhinitis:ti,ab,kw
#9.	eczema:ti,ab,kw
#10.	((food* or wheat or nut* or peanut* or milk or dairy or egg* or soy* or sesame or seed* or pecan* or pistachio* or walnut* or coconut* or fish or shellfish or seafood* or cereal* or gluten* or barley or corn* or maize) near/2 (sensitiv* or hypersensitiv* or allerg*)):ti,ab,kw
#11.	{or #2-#10}
#12.	#1 and #11

F.3.3 Symptoms in response to exercise

8. In people under investigation for asthma, what is the diagnostic accuracy of a clinical history of symptoms in response to exercise?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	History of symptoms following exercise	n/a	The following filter was used in all databases: DIAG1	See Table 24 English only Exclusion filter applied in Medline and Embase

Medline search terms

1.	medical history taking/
2.	(histories or history).ti,ab.
3.	exp questionnaires/

4.	question*.ti,ab.
5.	exp "signs and symptoms, respiratory"/
6.	(symptom or symptoms).ti,ab.
7.	or/1-6
8.	exp exercise/
9.	exp sports/
10.	(exercise* or sport*).ti,ab.
11.	(physical* adj (train* or exert* or activit*)).ti,ab.
12.	or/8-11
13.	7 and 12

Embase search terms

1.	exp *anamnesis/
2.	(histories or history).ti,ab.
3.	exp *questionnaire/
4.	question*.ti,ab.
5.	(symptom or symptoms).ti,ab.
6.	exp *breathing disorder/
7.	exp *coughing/
8.	or/1-7
9.	exp *exercise/
10.	exp *sport/
11.	(exercise* or sport*).ti,ab.
12.	(physical* adj (train* or exert* or activit*)).ti,ab.
13.	or/9-12
14.	8 and 13

Cochrane search terms

#1.	(histories or history or question*):ti,ab,kw
#2.	(symptom or symptoms):ti,ab,kw
#3.	{or #1-#2}
#4.	(exercise* or sport*):ti,ab,kw
#5.	(physical* near/1 (train* or exert* or activit*)):ti,ab,kw
#6.	#4or #5
#7.	#3 and #6

F.3.4 Symptoms after using medication

9. In people under investigation for asthma, what is the diagnostic accuracy of a clinical history of symptoms after taking the following drugs:
   - in adults - beta blockers, aspirin, or other NSAIDs
   - in children – ibuprofen?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all	Drugs as listed in	n/a	The following filter was	See Table 24

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
ages with asthma or suspected asthma	the question		used in all databases: DIAG1 The following filter was used in Medline and Embase only: DIAG2	English only Exclusion filter applied in Medline and Embase

Medline search terms

1.	((anti inflamm* or antiinflamm* or anti-inflamm*) adj2 (non- steroid* or nonsteroid* or non-steroid*) adj2 agent*).ti,ab.
2.	((cox2 or cox-2 or coxii or cox-ii) adj2 inhibitor*).ti,ab.
3.	((cyclo-oxygenase2 or cyclo-oxygenase-2 or cyclooxygenase-2 or cyclooxygenase2) adj2 inhibitor*).ti,ab.
4.	((cyclo-oxygenase-ii or cyclo-oxygenaseii or cyclooxygenase-ii or cyclooxygenaseii) adj2 inhibitor*).ti,ab.
5.	(arcoxia or lodine or eccoxolac or mobic or prexige).ti,ab.
6.	(diclofenac or naproxen or tolmetin or ketoprofen or aceclofenac).ti,ab.
7.	(fenbufen or tenoxicam or nabumetone or osmosin or benoxaprofen).ti,ab.
8.	(fenoprofen or azapropazone or aceclofenac or mefenamic acid or dexketoprofen).ti,ab.
9.	(ibuprofen or ibuprufen).ti,ab.
10.	(indometacin or indomethacin).ti,ab.
11.	(parecoxib or deracoxib or cimicoxib or tilmacoxib).ti,ab.
12.	(piroxicam or flurbiprofen or niflumic acid or diflunisal).ti,ab.
13.	(sulindac or meclofenamate or meclofenamic acid).ti,ab.
14.	exp anti-inflammatory agents, non-steroidal/
15.	celebrex.ti,ab.
16.	celecoxib.ti,ab.
17.	coxib*.ti,ab.
18.	etodolac.ti,ab.
19.	etoricoxib.ti,ab.
20.	exp aspirin/
21.	aspirin.ti,ab.
22.	exp cyclooxygenase 2 inhibitors/
23.	exp diclofenac/
24.	exp diflunisal/
25.	exp etodolac/
26.	exp fenoprofen/
27.	exp flurbiprofen/
28.	exp ibuprofen/
29.	exp indomethacin/
30.	exp ketoprofen/
31.	exp meclofenamic acid/
32.	exp mefenamic acid/
33.	exp naproxen/
34.	exp niflumic acid/

35.	exp piroxicam/
36.	exp sulindac/
37.	exp tolmetin/
38.	flosulide.ti,ab.
39.	iguratimod.ti,ab.
40.	meloxicam.ti,ab.
41.	nimesulide.ti,ab.
42.	nsaid*.ti,ab.
43.	tiaprofenic acid.ti,ab.
44.	(isoxicam or zomepirac or carprofen or proquazone or lornoxicam).ti,ab.
45.	(propranolol or angilol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim).ti,ab.
46.	(beta adj3 block*).ti,ab.
47.	(b adj3 block*).ti,ab.
48.	(beta adj2 antagonist*).ti,ab.
49.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) adj3 (blockade or blocker*or blocking or antagonist*)).ti,ab.
50.	exp adrenergic beta-antagonists/
51.	or/1-50
52.	medical history taking/
53.	(histories or history).ti,ab.
54.	exp drug hypersensitivity/
55.	((drug or medication* or medicine*) adj2 (allerg* or hypersensitivity or sensitivity or intolerance)).ti,ab.
56.	exp questionnaires/
57.	question*.ti,ab.
58.	exp "signs and symptoms, respiratory"/
59.	(symptom or symptoms).ti,ab.
60.	or/52-59
61.	51 and 60

Embase search terms

1.	((anti inflamm* or antiinflamm* or anti-inflamm*) adj2 (non- steroid* or nonsteroid* or non-steroid*) adj2 agent*).ti,ab.
2.	((cox2 or cox-2 or coxii or cox-ii) adj2 inhibitor*).ti,ab.
3.	((cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase 2) adj2 inhibitor*).ti,ab.
4.	((cyclooxygenase-ii or cyclooxygenaseii or cyclooxygenase ii) adj2 inhibitor*).ti,ab.
5.	(arcoxia or lodine or eccoxolac or prexige or mobic).ti,ab.
6.	(diclofenac or naproxen or tolmetin or ketoprofen or aceclofenac).ti,ab.
7.	(fenbufen or tenoxicam or nabumetone or osmosin or benoxaprofen).ti,ab.
8.	(fenoprofen or azapropazone or aceclofenac or mefenamic acid or dexketoprofen).ti,ab.
9.	(ibuprofen or ibuprufen).ti,ab.
10.	(indometacin or indomethacin).ti,ab.

11.	(isoxicam or zomepirac or carprofen or proquazone or lornoxicam).ti,ab.
12.	(parecoxib or deracoxib or cimicoxib or tilmacoxib).ti,ab.
13.	(piroxicam or flurbiprofen or niflumic acid or diflunisal).ti,ab.
14.	(sulindac or meclofenamate or meclofenamic acid).ti,ab.
15.	celebrex.ti,ab.
16.	celecoxib.ti,ab.
17.	coxib*.ti,ab.
18.	etodolac.ti,ab.
19.	etoricoxib.ti,ab.
20.	exp *aceclofenac/
21.	exp *aspirin/
22.	exp *azapropazone/
23.	exp *benoxaprofen/
24.	exp *carprofen/
25.	exp *celecoxib/
26.	exp *cyclooxygenase 2 inhibitor/
27.	exp *dexketoprofen/
28.	exp *diclofenac/
29.	exp *diflunisal/
30.	exp *etodolac/
31.	exp *etoricoxib/
32.	exp *fenbufen/
33.	exp *fenoprofen/
34.	exp *flosulide/
35.	exp *flurbiprofen/
36.	exp *ibuprofen/
37.	exp *iguratimod/
38.	exp *indomethacin/
39.	exp *ketoprofen/
40.	exp *lornoxicam/
41.	exp *lumiracoxib/
42.	exp *meclofenamic acid/
43.	exp *mefenamic acid/
44.	exp *meloxicam/
45.	exp *nabumetone/
46.	exp *naproxen/
47.	exp *niflumic acid/
48.	exp *nimesulide/
49.	exp *parecoxib/ or exp *tilmacoxib/
50.	exp *piroxicam/
51.	exp *proquazone/
52.	exp *sulindac/
53.	exp *tenoxicam/
54.	exp *tiaprofenic acid/
55.	exp *tolmetin/

56.	exp *zomepirac/
57.	flosulide.ti,ab.
58.	iguratimod.ti,ab.
59.	lumiracoxib.ti,ab.
60.	meloxicam.ti,ab.
61.	nimesulide.ti,ab.
62.	exp *nonsteroid antiinflammatory agent/
63.	nsaid*.ti,ab.
64.	tiaprofenic acid.ti,ab.
65.	aspirin.ti,ab.
66.	exp *beta adrenergic receptor blocking agent/
67.	exp *bisoprolol/ or exp *bisoprolol fumarate/ or exp *bisoprolol fumarate plus hydrochlorothiazide/ or exp *carvedilol/ or exp *metoprolol/ or exp*metoprolol fumarate/ or exp *metoprolol succinate/ or exp *metoprolol tartrate/ or exp *nebivolol/
68.	(propranolol or angilol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim).ti,ab.
69.	(beta adj3 block*).ti,ab.
70.	(b adj3 block*).ti,ab.
71.	(beta adj2 antagonist*).ti,ab.
72.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) adj3 (blockade or blocker* or blocking or antagonist*)).ti,ab.
73.	or/1-72
74.	exp *anamnesis/
75.	(histories or history).ti,ab.
76.	exp *questionnaire/
77.	question*.ti,ab.
78.	exp *drug hypersensitivity/
79.	((drug or medication* or medicine*) adj2 (allerg* or hypersensitivity or sensitivity or intolerance)).ti,ab.
80.	(symptom or symptoms).ti,ab.
81.	exp *breathing disorder/
82.	exp *coughing/
83.	or/74-82
84.	73 and 83

Cochrane search terms

#1.	((anti inflamm* or antiinflamm* or anti-inflamm*) near/2 (non- steroid* or nonsteroid* or non-steroid*)):ti,ab,kw
#2.	((cox2 or cox-2 or coxii or cox-ii) near/2 (inhibitor*)):ti,ab,kw
#3.	((cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase 2) near/2 (inhibitor*)):ti,ab,kw
#4.	((cyclo-oxygenase2 or cyclo-oxygenase-2 or cyclooxygenase-2 or cyclooxygenase2) near/2 (inhibitor*)):ti,ab,kw
#5.	((cyclooxygenase-ii or cyclooxygenaseii) near/2 (inhibitor*)):ti,ab,kw
#6.	((cyclo-oxygenase-ii or cyclo-oxygenaseii or cyclooxygenase-ii or cyclooxygenaseii) near/2

	(inhibitor*)):ti,ab,kw
#7.	(aceclofenac or arcoxia or aspirin or azapropazone or benoxaprofen or carprofen or celebrex or celecoxib or cimicoxib or coxib* or deracoxib or dexketoprofen or diclofenac or diflunisal or eccoxolac or etodolac or etoricoxib or fenbufen or fenoprofen or flosulide or flurbiprofen or ibuprofen or ibuprufen or iguratimod or indometacin or indomethacin or isoxicam or ketoprofen or lodine or lornoxicam or lumiracoxib or meclofenam* or mefenamic acid or meloxicam or mobic or nabumetone or naproxen or niflumic acid or nimesulide or nsaid* or osmosin or parecoxib or piroxicam or prexige or proquazone or sulindac or tenoxicam or tiaprofenic acid or tilmacoxib or tolmetin or zomepirac):ti,ab,kw
#8.	(propranolol or angilol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim):ti,ab,kw
#9.	(beta or b) near/3 (block* or antagonist*):ti,ab,kw
#10.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) near/3 (blockade or blocker*or blocking or antagonist*)):ti,ab,kw
#11.	{or #1-#10}
#12.	(histories or history or question*):ti,ab,kw
#13.	((drug or medication* or medicine*) near/2 (allerg* or hypersensitivity or sensitivity or intolerance)):ti,ab,kw
#14.	(symptom or symptoms):ti,ab,kw
#15.	{or #12-#14}
#16.	#11 and #15

F.3.5 Occupational asthma

10. In adults under investigation for occupational asthma, what is the diagnostic accuracy for case identification, of asking whether their symptoms are better away from work?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
Adults under investigation for occupational asthma	Symptom history	n/a	The following filters were used in Medline and Embase only: DIAG1, OBS, RCT, SR	See Table 24 English only Exclusion filter applied in Medline and Embase

Medline search terms

1.	asthma, occupational/
2.	((occupation* or work* or job* or employ*) adj2 asthma*).ti,ab
3.	or/1-2
4.	*occupational diseases/
5.	exp asthma/
6.	4 and 5
7.	3 or 6
8.	medical history taking/
9.	(histories or history).ti,ab.

10.	questionnaires/
11.	question*.ti,ab.
12.	(holiday* or weekend* or vacation*).ti,ab.
13.	((away or absent* or leave*) adj3 (work* or job* or employ* or occupation*)).ti,ab.
14.	or/8-13
15.	7 and 14

Embase search terms

1.	((occupation* or work* or job* or employ*) adj2 asthma*).ti,ab.
2.	*occupational asthma/
3.	or/1-2
4.	*occupational disease/
5.	exp *asthma/
6.	4 and 5
7.	3 or 6
8.	exp *anamnesis/
9.	(histories or history).ti,ab.
10.	exp *questionnaire/
11.	question*.ti,ab.
12.	(holiday* or weekend* or vacation*).ti,ab.
13.	((away or absent* or leave*) adj3 (work* or job* or employ* or occupation*)).ti,ab.
14.	or/8-13
15.	7 and 14

Cochrane search terms

#1.	((occupation* or work* or job* or employ*) near/2 asthma*):ti,ab,kw
#2.	(histories or history or question* or holiday* or weekend* or vacation*):ti,ab,kw
#3.	((away or absent* or leave*) near/3 (work* or job* or employ* or occupation*)):ti,ab,kw
#4.	#2 or #3
#5.	#1 and #4

F.3.6 Spirometry/flow volume loop measures

11. In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of spirometry / flow volume loop measures?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Spirometry / flow volume loop measures	n/a	The following filter was used in all databases: DIAG1	See Table 24 English only Exclusion filter applied in Medline and Embase

Medline search terms

1.	vital capacity/

2.	forced expiratory volume/
3.	(FEV1 or FEV 1 or FVC).ti,ab.
4.	(flow volume adj (loop* or curve* or graph*)).ti,ab.
5.	(forced expiratory volume* adj6 ("1" or one)).ti,ab.
6.	((force* or time*) adj vital capacit*).ti,ab.
7.	spirometry.ti.
8.	or/1-7

Embase search terms

1.	vital capacity/
2.	forced expiratory volume/
3.	lung flow volume curve/
4.	(FEV1 or FEV 1 or FVC).ti,ab.
5.	(flow volume adj (loop* or curve* or graph*)).ti,ab.
6.	(forced expiratory volume* adj6 ("1" or one)).ti,ab.
7.	((force* or time*) adj vital capacit*).ti,ab.
8.	spirometry.ti.
9.	or/1-8

Cochrane search terms

#1.	MeSH descriptor: [Vital Capacity] this term only
#2.	MeSH descriptor: [Forced Expiratory Volume] this term only
#3.	(FEV1 or "FEV 1" or FVC):ti,ab
#4.	(flow volume near/2 (loop* or curve* or graph*)):ti,ab
#5.	(forced expiratory volume* near/6 ("1" or one)):ti,ab
#6.	((force* or time*) near/2 vital capacit*):ti,ab
#7.	spirometry:ti
#8.	{or #1-#7}

F.3.7 Bronchodilator response

12. In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of bronchodilator response (using PEF or FEV1)?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Bronchodilator response	n/a	The following filter was used in Medline and Cochrane: DIAG1 The following filter was used in Medline only: DIAG2	See Table 24 English only Exclusion filter applied in Medline and Embase

Medline search terms

1.	exp bronchodilator agents/du
2.	bronchoreversibility.ti,ab.
3.	((bronchodilator* or bronchial dilat* or broncholytic*) adj3 (test* or revers* or respons* or

	respond*)).ti,ab.
4.	(BDR or BDT).ti,ab.
5.	or/1-4

Embase search terms

1.	bronchoreversibility.ti,ab.
2.	((bronchodilator* or bronchial dilat* or broncholytic*) adj3 (test* or revers* or respons* or respond*)).ti,ab.
3.	(BDR or BDT).ti,ab.
4.	bronchoreversibility.ti,ab.
5.	or/1-4
6.	exp "sensitivity and specificity"/
7.	(sensitivity or specificity).ti,ab.
8.	((pre test or pretest or post test) adj probability).ti,ab.
9.	(predictive value* or PPV or NPV).ti,ab.
10.	likelihood ratio*.ti,ab.
11.	(ROC curve* or AUC).ti,ab.
12.	(diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
13.	diagnostic accuracy/
14.	diagnostic test accuracy study/
15.	gold standard.ab.
16.	sensitiv*.mp.
17.	diagnos*.mp.
18.	di.fs.
19.	or/6-18
20.	5 and 19
21.	exp *bronchodilating agent/
22.	or/6-15
23.	21 and 22
24.	20 or 23

Cochrane search terms

#1.	((bronchodilator* or bronchial dilat* or broncholytic*) near/3 (test* or revers* or respons* or respond*)):ti,ab,kw
#2.	bronchoreversibility:ti,ab,kw
#3.	(BDR or BDT):ti,ab,kw
#4.	MeSH descriptor: [Bronchodilator Agents] explode all trees and with qualifiers: [Diagnostic use - DU]
#5.	{or #1-#4}

F.3.8 Peak expiratory flow

13. In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of peak expiratory flow (PEF) variability?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Peak expiratory flow (PEF) variability	n/a	The following filter was used in all databases: DIAG1 The following filter was used in Medline and Embase only: DIAG2	See Table 24 English only Exclusion filter applied in Medline and Embase

Medline search terms

1.	PEFV.ti,ab.
2.	((diurnal* or circadian or variation* or variability or fluctuat* or alter* or increas* or decreas* or chang*) adj3 (PEF or PEFR or PFR or peak expiratory flow* or peak flow*)).ti,ab.
3.	peak expiratory flow rate/
4.	exp circadian rhythm/
5.	3 and 4
6.	1 or 2 or 5

Embase search terms

1.	PEFV.ti,ab.
2.	((diurnal* or circadian or variation* or variability or fluctuat* or alter* or increas* or decreas* or chang*) adj3 (PEF or PEFR or PFR or peak expiratory flow* or peak flow*)).ti,ab.
3.	peak expiratory flow/
4.	circadian rhythm/
5.	3 and 4
6.	1 or 2 or 5

Cochrane search terms

#1.	pefv:ti,ab,kw
#2.	((diurnal* or circadian or variation* or variability or fluctuat* or alter* or increas* or decreas* or chang*) near/3 (PEFR or PFR or peak expiratory flow* or peak flow*)):ti,ab,kw
#3.	{or #1-#2}

F.3.9 Skin prick test

14. In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of skin prick tests?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Skin prick test	n/a	The following filter was used in Medline and Embase only: DIAG1	See Table 24 English only Exclusion filter applied in Medline and Embase

Medline search terms

1.	((dust or housedust) adj mite*).ti,ab.

2.	(dermatophagoides or euroglyphus).ti,ab.
3.	pyroglyphidae/
4.	(cat or cats or feline*).ti,ab.
5.	cats/
6.	(dog or dogs or canine*).ti,ab.
7.	dogs/
8.	pollen*.ti,ab.
9.	pollen/
10.	exp aspergillus/
11.	aspergillus.ti,ab.
12.	alternaria/
13.	alternaria.ti,ab.
14.	cladosporium/
15.	cladosporium.ti,ab.
16.	((air* or aero*) adj allergen*).ti,ab.
17.	aeroallergen*.ti,ab.
18.	or/1-17
19.	exp skin tests/
20.	skin prick*.ti,ab.
21.	skin scratch*.ti,ab.
22.	prick* test*.ti,ab.
23.	scratch* test*.ti,ab.
24.	skin test*.ti,ab.
25.	or/19-24
26.	18 and 25

Embase search terms

1.	((dust or housedust) adj mite*).ti,ab.
2.	(dermatophagoides or euroglyphus).ti,ab.
3.	(cat or cats or feline*).ti,ab.
4.	(dog or dogs or canine*).ti,ab.
5.	pollen*.ti,ab.
6.	aspergillus.ti,ab.
7.	alternaria.ti,ab.
8.	cladosporium.ti,ab.
9.	exp *dermatophagoides/
10.	*cat/
11.	*dog/
12.	*grass pollen/
13.	*pollen/
14.	exp *aspergillus/
15.	exp *alternaria/
16.	exp *cladosporium/
17.	((air* or aero*) adj allergen*).ti,ab.
18.	aeroallergen*.ti,ab.

19.	or/1-18
20.	exp *skin test/
21.	skin prick*.ti,ab.
22.	skin scratch*.ti,ab.
23.	prick* test*.ti,ab.
24.	scratch* test*.ti,ab.
25.	skin test*.ti,ab.
26.	or/20-25
27.	19 and 26

Cochrane search terms

#1.	(skin prick* or skin scratch* or prick* test* or scratch* test* or skin test*):ti,ab,kw
#2.	((dust or housedust) near/1 mite*):ti,ab,kw
#3.	(dermatophagoides or euroglyphus or cat or cats or feline* or dog or dogs or canine* or pollen or aspergillus or alternaria or cladosporium or pyroglyphidae):ti,ab,kw
#4.	((air* or aero*) near/1 allergen*):ti,ab
#5.	aeroallergen*:ti,ab
#6.	{or #2-#5}
#7.	#1 and #6

F.3.10 IgE

15. In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of total and specific serum IgE measures?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Serum IgE	n/a	The following filters were used in Medline and Embase only: DIAG1, OBS, RCT, SR	See Table 24 English only Exclusion filter applied in Medline and Embase

Medline and Embase search terms

1.	*radioallergosorbent test/
2.	(RAST or radioallergosorbent).ti.
3.	*immunoglobulin E/
4.	(immunoglobulin E or IgE).ti.
5.	or/1-4

Cochrane search terms

#1.	(immunoglobulin E or IgE or RAST or radioallergosorbent):ti,kw

F.3.11 FeNO

16. In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of fractional exhaled nitric oxide (FeNO) measures?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Fractional exhaled nitric oxide (FeNO)	n/a	The following filter was used in Medline and Embase only: DIAG1	See Table 24 English only Exclusion filter applied in Medline and Embase

Medline search terms

1.	FeNO.ti,ab.
2.	((Fe or exhal* or fraction*) adj2 (NO or nitric or nitrogen)).ti,ab.
3.	or/1-2
4.	nitric oxide/
5.	biological markers/
6.	breath tests/
7.	exhalation/
8.	or/5-7
9.	4 and 8
10.	3 or 9

Embase search terms

1.	FeNO.ti,ab.
2.	((Fe or exhal* or fraction*) adj2 (NO or nitric or nitrogen)).ti,ab.
3.	or/1-2
4.	*nitric oxide/
5.	*breath analysis/
6.	*expired air/
7.	*biological marker/
8.	*exhalation/
9.	or/5-8
10.	4 and 9
11.	3 or 10

Cochrane search terms

#1.	FeNO:ti,ab,kw
#2.	((Fe or exhal* or fraction*) near/2 (NO or nitric or nitrogen)):ti,ab,kw
#3.	((NO or nitric or nitrogen) near/2 (marker* or biomarker* or breath* or
#4.	{or #1-#3}
#5.	test* or exhal* or expir*)):ti,ab,kw
#6.	MeSH descriptor: [Nitric Oxide] explode all trees
#7.	MeSH descriptor: [Biological Markers] explode all trees
#8.	MeSH descriptor: [Breath Tests] explode all trees
#9.	MeSH descriptor: [Exhalation] explode all trees
#10.	{or #6-#9}
#11.	#5 and #10

#12.	#4 or #11

F.3.12 Peripheral blood eosinophil count

17. In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of eosinophil blood count measures?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Eosinophil blood count measures	n/a	The following filter was used in Medline and Embase only: DIAG1	See Table 24 English only Exclusion filter applied in Medline and Embase

Medline search terms

1.	*eosinophils/
2.	*eosinophilia/
3.	(blood* adj2 (eosinophil* or acidophil*)).ti,ab.
4.	or/1-3

Embase search terms

1.	*eosinophil/
2.	*eosinophil count/
3.	*eosinophilia/
4.	(blood* adj2 (eosinophil* or acidophil*)).ti,ab.
5.	or/1-4

Cochrane search terms

#1.	eosinophil*:kw
#2.	(blood* near/2 (eosinophil* or acidophil*)):ti,ab
#3.	{or #1-#2}

F.3.13 Bronchial challenge test: histamine, methacholine, mannitol

Searches for the following two questions were run as one search:

18. In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of airway hyper-reactivity (non-specific bronchial challenge) with histamine and methacholine?
19. In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of airway hyper-reactivity (non-specific bronchial challenge) with mannitol?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or	Bronchial challenge tests using histamine and	n/a	The following filter was used in all databases: DIAG1	See Table 24 English only Exclusion filter

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
suspected asthma	methacholine or mannitol			applied in Medline and Embase

Medline search terms

1.	exp mannitol/
2.	exp histamine/
3.	methacholine chloride/
4.	(mannitol* or histamine* or methacholine*).ti,ab.
5.	or/1-4
6.	bronchial provocation tests/
7.	(inhalation or provocation or provoke* or challenge*).ti,ab.
8.	(hyperresponsiv* or hyperreactiv*).ti,ab.
9.	bronchial hyperreactivity/
10.	or/6-9
11.	5 and 10

Embase search terms

1.	mannitol/
2.	histamine/
3.	methacholine/
4.	(mannitol* or histamine* or methcholine*).ti,ab.
5.	or/1-4
6.	inhalation test/
7.	provocation test/
8.	bronchus hyperreactivity/
9.	(inhalation or provocation or provoke* or challenge*).ti,ab.
10.	(hyperresponsiv* or hyperreactiv*).ti,ab.
11.	or/6-10
12.	5 and 11

Cochrane search terms

#1.	MeSH descriptor: [Mannitol] explode all trees
#2.	MeSH descriptor: [Histamine] explode all trees
#3.	MeSH descriptor: [Methacholine Chloride] explode all trees
#4.	(mannitol or histamine or methacholine):ti,ab
#5.	{or #1-#4}
#6.	MeSH descriptor: [Bronchial Provocation Tests] explode all trees
#7.	MeSH descriptor: [Bronchial Hyperreactivity] explode all trees
#8.	(inhalation or provocation or provoke* or challenge*):ti,ab
#9.	(hyperresponsiv* or hyperreactiv*):ti,ab
#10.	{or #6-#9}
#11.	5 and 10

F.3.14 Bronchial challenge test: exercise

20. In people under investigation for asthma, what is the diagnostic accuracy of bronchoconstriction in response to an exercise challenge?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Clinical history of symptoms in response to exercise	n/a	The following filter was used in all databases: DIAG1	See Table 24 English only Exclusion filter applied in Medline and Embase

Medline search terms

1.	exp exercise/
2.	exp sports/
3.	(exercise* or sport*).ti,ab.
4.	(physical* adj (train* or exert* or activit*)).ti,ab.
5.	or/1-4
6.	medical history taking/
7.	(histories or history).ti,ab.
8.	exp questionnaires/
9.	question*.ti,ab.
10.	exp "signs and symptoms, respiratory"/
11.	(symptom or symptoms).ti,ab.
12.	or/6-11
13.	5 and 12

Embase search terms

1.	exp *exercise/
2.	exp *sport/
3.	(exercise* or sport*).ti,ab.
4.	(physical* adj (train* or exert* or activit*)).ti,ab.
5.	or/1-4
6.	exp *anamnesis/
7.	(histories or history).ti,ab.
8.	exp *questionnaire/
9.	question*.ti,ab.
10.	(symptom or symptoms).ti,ab.
11.	exp *breathing disorder/
12.	exp *coughing/
13.	or/6-12
14.	5 and 13

Cochrane search terms

#1.	(exercise* or sport*):ti,ab,kw

#2.	(physical* near/1 (train* or exert* or activit*)):ti,ab,kw
#3.	{or #1-#2}
#4.	(histories or history or question*):ti,ab,kw
#5.	(symptom or symptoms):ti,ab,kw
#6.	#4 or #5
#7.	#3 and #6

F.3.15 Questionnaires

21. In people with asthma, what is the clinical and cost-effectiveness of using symptom scores/diaries or validated questionnaires measuring symptom control (e.g. ACT, ACQ, cACT, RCP 3 questions) and/or health related quality of life (e.g. AQLQ, pAQLQ) to monitor asthma?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Validated questionnaires	n/a	The following filters were used in Medline and Embase only: OBS, RCT, VAL	See Table 24 English only Exclusion filter applied in Medline and Embase

Medline search terms

1.	(diary or diaries).ti,ab.
2.	(symptom* adj2 scor*).ti,ab.
3.	or/1-2
4.	(measur* or assess* or monitor* or evaluat*).ti,ab.
5.	3 and 4
6.	(CACT or ACQ 6 or ACQ 7 or ACQ6 or ACQ7 or PACQ or RCP-3 or RCP3 or PAQLQ or AQLQ or PACQLQ).ti,ab.
7.	asthma control test*.ti,ab.
8.	asthma control questionnaire*.ti,ab.
9.	(rcp3 question* or rcp 3 question* or rcp three question* or royal college of physician*3 question* or royal college of physician* three question*).ti,ab.
10.	asthma quality of life questionnaire*.ti,ab.
11.	((p?ediatric or caregiver* or care giver* or carer*) adj3 quality of life questionnaire*).ti,ab.
12.	or/6-11
13.	5 or 12

Embase search terms

1.	(diary or diaries).ti,ab.
2.	(symptom* adj2 scor*).ti,ab.
3.	or/1-2
4.	(measur* or assess* or monitor* or evaluat*).ti,ab.
5.	3 and 4
6.	(CACT or ACQ 6 or ACQ 7 or ACQ6 or ACQ7 or PACQ or RCP-3 or RCP3 or PAQLQ or AQLQ or PACQLQ).ti,ab.
7.	asthma control test*.ti,ab.

8.	asthma control questionnaire*.ti,ab.
9.	(rcp3 question* or rcp 3 question* or rcp three question* or royal college of physician*3 question* or royal college of physician* three question*).ti,ab.
10.	asthma quality of life questionnaire*.ti,ab.
11.	((p?ediatric or caregiver* or care giver* or carer*) adj3 quality of life questionnaire*).ti,ab.
12.	or/6-11
13.	5 or 12

Cochrane search terms

#1.	(diary or diaries):ti,ab
#2.	(symptom* near/2 scor*):ti,ab
#3.	{or #1-#2}
#4.	(measur* or assess* or monitor* or evaluat*):ti,ab
#5.	#3 and #4
#6.	(CACT or ACQ 6 or ACQ 7 or ACQ6 or ACQ7 or PACQ or RCP-3 or RCP3 or PAQLQ or AQLQ or PACQLQ):ti,ab
#7.	asthma control test*:ti,ab
#8.	asthma control questionnaire*:ti,ab
#9.	(rcp3 question* or rcp 3 question* or rcp three question* or royal college of physician*3 question* or royal college of physician* three question*):ti,ab
#10.	asthma quality of life questionnaire*:ti,ab
#11.	((p?ediatric or caregiver* or care giver* or carer*) near/3 "quality of life questionnaire*"):ti,ab
#12.	{or #6-#11}
#13.	#5 or #12

F.3.16 Lung functions tests

22. In people with asthma, what is the clinical and cost-effectiveness of using measures of pulmonary function assessing asthma control (for example, spirometry and peak expiratory flow) to monitor asthma?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Lung function tests	n/a	The following filter was used in Medline and Embase only: RCT	See Table 24 English only Exclusion filter applied in Medline and Embase

Medline search terms

1.	vital capacity/
2.	forced expiratory volume/
3.	(FEV1 or FEV 1 or FVC).ti,ab.
4.	(flow volume adj (loop* or curve* or graph*)).ti,ab.
5.	(forced expiratory volume* adj6 ("1" or one)).ti,ab.
6.	((force* or time*) adj vital capacit*).ti,ab.
7.	spirometry.ti.

8.	or/1-7
9.	PEFV.ti,ab.
10.	(PEF or PEFR or PFR or peak expiratory flow* or peak flow*).ti,ab.
11.	peak expiratory flow rate/
12.	or/9-11
13.	8 or 12
14.	monitoring, physiologic/
15.	monitor*.ti,ab.
16.	self care/
17.	plan*.ti,ab.
18.	or/14-17
19.	13 and 18

Embase search terms

1.	vital capacity/
2.	forced expiratory volume/
3.	lung flow volume curve/
4.	(FEV1 or FEV 1 or FVC).ti,ab.
5.	(flow volume adj (loop* or curve* or graph*)).ti,ab.
6.	(forced expiratory volume* adj6 ("1" or one)).ti,ab.
7.	((force* or time*) adj vital capacit*).ti,ab.
8.	spirometry.ti.
9.	or/1-8
10.	PEFV.ti,ab.
11.	(PEF or PEFR or PFR or peak expiratory flow* or peak flow*).ti,ab.
12.	peak expiratory flow/
13.	or/10-12
14.	(monitor* or plan*).ti,ab.
15.	exp monitoring/
16.	self care/
17.	or/14-16
18.	9 or 13
19.	17 and 18

Cochrane search terms

#1.	MeSH descriptor: [Vital Capacity] this term only
#2.	MeSH descriptor: [Forced Expiratory Volume] this term only
#3.	(FEV1 or "FEV 1" or FVC):ti,ab
#4.	(flow volume near/2 (loop* or curve* or graph*)):ti,ab
#5.	(forced expiratory volume* near/6 ("1" or one)):ti,ab
#6.	((force* or time*) near/2 vital capacit*):ti,ab
#7.	spirometry:ti
#8.	{or #1-#7}
#9.	PEFV:ti,ab
#10.	(PEF or PEFR or PFR or peak expiratory flow* or peak flow*):ti,ab,kw
#11.	#9 or #10

#12.	#8 or #11
#13.	(monitor* or plan*):ti,ab,kw
#14.	MeSH descriptor: [Self Care] explode all trees
#15.	#13 or #14
#16.	#12 and #15

F.3.17 FeNO (monitoring)

For search terms see F.3.11

23. In people with asthma, what is the clinical and cost-effectiveness of using fractional exhaled nitric oxide (FeNO) measures for monitoring asthma control?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Fractional exhaled nitric oxide (FeNO)	n/a	The following filters were used in Medline and Embase only: OBS, RCT, SR	See Table 24 English only Exclusion filter applied in Medline and Embase

F.3.18 Peripheral blood eosinophil count (monitoring)

For search terms see F.3.12

24. In people with asthma, what is the clinical and cost-effectiveness of using the peripheral blood eosinophil count for monitoring asthma control?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Eosinophil blood count measures	n/a	The following filters were used in Medline and Embase only: OBS, RCT	See Table 24 English only Exclusion filter applied in Medline and Embase

F.3.19 Airway hyper-reactivity measures

For search terms see F.3.13

25. In people with asthma, what is the clinical and cost-effectiveness of using indirect challenge tests with mannitol or direct challenge tests with histamine or methacholine for monitoring asthma control?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all	Bronchial challenge	n/a	The following filter was	See Table 24

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
ages with asthma or suspected asthma	tests using histamine and methacholine or mannitol		used in Medline and Embase only: RCT	English only Exclusion filter applied in Medline and Embase

F.3.20 Adherence to treatment

26. In people with asthma, what is the clinical and cost-effectiveness of monitoring adherence to treatment?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Strategies to monitor or interventions to increase adherence	n/a	The following filters were used in Medline and Embase only: OBS, RCT	See Table 24 English only Exclusion filter applied in Medline and Embase

Medline search terms

1.	(adheren* or complian* or concordan* or nonadheren* or noncomplian*).ti,ab.
2.	exp patient compliance/
3.	or/1-2
4.	FeNO.ti,ab.
5.	nitric oxide/
6.	biological markers/
7.	breath tests/
8.	exhalation/
9.	or/6-8
10.	5 and 9
11.	((Fe or exhal* or fraction*) adj2 (NO or nitric or nitrogen)).ti,ab.
12.	4 or 10 or 11
13.	prescription*.ti,ab.
14.	exp pharmaceutical services/
15.	or/13-14
16.	((electronic adj2 inhaler*) or smartinhaler* or smart inhaler*).ti,ab.
17.	prednisolone.ti,ab.
18.	theophylline.ti,ab.
19.	(MARS or (medication adherence adj2 scale*)).ti,ab.
20.	exp adrenal cortex hormones/
21.	administration, inhalation/
22.	20 and 21
23.	(inhal* and (corticosteroid* or steroid* or corticoid* or glucocorticoid* or gluco-cortico*)).ti,ab.

24.	22 or 23
25.	or/12,15-19,24
26.	exp monitoring, physiologic/
27.	monitor*.ti,ab.
28.	or/26-27
29.	25 or 28
30.	3 and 29

Embase search terms

1.	(adheren* or complian* or concordan* or nonadheren* or noncomplian*).ti,ab.
2.	exp *patient compliance/
3.	or/1-2
4.	FeNO.ti,ab.
5.	((Fe or exhal* or fraction*) adj2 (NO or nitric or nitrogen)).ti,ab.
6.	*nitric oxide/
7.	*breath analysis/
8.	*expired air/
9.	*biological marker/
10.	*exhalation/
11.	or/7-10
12.	6 and 11
13.	4 or 5 or 12
14.	prescription*.ti,ab.
15.	*pharmacy/
16.	*prescription/
17.	((electronic adj2 inhaler*) or smartinhaler* or smart inhaler*).ti,ab.
18.	prednisolone.ti,ab.
19.	theophylline.ti,ab.
20.	*prednisolone/
21.	*theophylline blood level/
22.	(MARS or (medication adherence adj2 scale*)).ti,ab.
23.	exp *corticosteroid/ih
24.	(inhal* and (corticosteroid* or steroid* or corticoid* or glucocorticoid* or gluco-cortico*)).ti,ab.
25.	or/13-24
26.	exp *monitoring/
27.	monitor*.ti,ab.
28.	or/26-27
29.	3 and (25 or 28)

Cochrane search terms

#1.	(adheren* or complian* or concordan* or nonadheren* or noncomplian*):ti,ab
#2.	[mh ^"patient compliance"]
#3.	{or #1-#2}
#4.	FeNO:ti,ab
#5.	((Fe or exhal* or fraction*) near/2 (NO or nitric or nitrogen)):ti,ab

#6.	((NO or nitric or nitrogen) near/2 (marker* or biomarker* or breath* or test* or exhal* or expir*)):ti,ab
#7.	[mh ^"Nitric Oxide"]
#8.	[mh ^"Biological Markers"]
#9.	[mh ^"Breath Tests"]
#10.	[mh ^Exhalation]
#11.	{or #8-#10}
#12.	#7 and #11
#13.	{or #4-#6, #12}
#14.	prescription*:ti,ab
#15.	[mh ^"pharmaceutical services"]
#16.	((electronic near/2 inhaler*) or smartinhaler* or smart inhaler*):ti,ab
#17.	prednisolone:ti,ab
#18.	theophylline:ti,ab
#19.	(MARS or medication adherence):ti,ab
#20.	[mh ^"adrenal cortex hormones"]
#21.	[mh "administration, inhalation"]
#22.	(inhal* and (corticosteroid* or steroid* or corticoid* or glucocorticoid* or gluco-cortico*)):ti,ab
#23.	#20 and #21
#24.	{or #13-#19, #22-#23}
#25.	[mh ^"Monitoring, Physiologic"]
#26.	monitor*:ti,ab
#27.	{or #25-#36}
#28.	#3 and (#24 or #27)

F.3.21 Inhaler technique

27. In people with asthma, what is the optimal frequency and method for monitoring inhaler technique?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Monitoring inhaler technique	n/a	The following filters were used in Medline and Embase only: OBS, RCT	See Table 24 English only Exclusion filter applied in Medline and Embase

Medline search terms

1.	((nebuliser* or nebulizer* or vaporiser* or vaporizer* or atomiser* or atomizer* or inhal* or aerosol* or device*) adj5 (technique* or competen* or efficien* or inefficien* or misuse* or check* or correct* or incorrect* or evaluat* or adher*)).ti,ab.

Embase search terms

1.	((nebuliser* or nebulizer* or vaporiser* or vaporizer* or atomiser* or atomizer* or inhal* or aerosol* or device*) adj5 (technique* or competen* or efficien* or inefficien* or misuse* or

	check* or correct* or incorrect* or evaluat* or adher*)).ti,ab.

Cochrane search terms

#1.	((nebuliser* or nebulizer* or vaporiser* or vaporizer* or atomiser* or atomizer* or inhal* or aerosol* or device*) near/5 (technique* or competen* or efficien* or inefficien* or misuse* or check* or correct* or incorrect* or evaluat* or adher*)):ti,ab

F.3.22 Tele-healthcare

Searches for the following question were undertaken by the Cochrane Airways Group using the Cochrane Airways Group Specialised Register of trials. Full search methodology is provided in the published Cochrane review.[1111]

28. In people with asthma, what is the clinical and cost-effectiveness of tele-healthcare to monitor asthma control?

F.4 Health economics search

F.4.1 Health economic reviews

Economic searches were conducted in Medline, Embase, HEED and CRD for NHS EED and HTA.

Population	Intervention or exposure	Comparison	Study design filters	Date parameters and other limits
People of all ages with asthma or suspected asthma	n/a	n/a	The following filters were used in Medline and Embase only: HE	Medline and Embase 2012–1 October 2014 CRD EED and HTA All dates to 1 October 2014 English only

Medline and Embase search terms

4.	exp asthma/
5.	asthma*.ti.ab.
6.	or/1-2

Cochrane search terms

#4.	MeSH descriptor: [Asthma] explode all trees
#5.	asthma*:ti,ab.
#6.	{or #1-#2}

CRD search terms

#1.	MeSH DESCRIPTOR Asthma EXPLODE ALL TREES
#2.	(asthma*)
#3.	#1 OR #2

HEED search terms

1.	AX=asthma*

F.4.2 Quality of life reviews

Quality of life searches were conducted in Medline and Embase only

Population	Intervention or exposure	Comparison	Study design filters	Date parameters and other limits
People of all ages with asthma or suspected asthma	n/a	n/a	The following filters were used in Medline and Embase only: QOL	Medline 1948-02/10/2014 Embase 1980–02/10/2014 English only

Appendix G: Clinical evidence tables

G.1 Signs and symptoms for diagnosis

Table 25: CHOI 2007[315]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
Choi et al., 2007. Easy diagnosis of asthma: computer-assisted, symptom-based diagnosis. Journal of Korean Medical Science: 22: 832-838. REF ID: CHOI2007	<u>Study type:</u> Diagnostic cross sectional study <u>Setting:</u> Hospital outpatient dept. <u>Country:</u> Korea <u>Recruitment:</u> Consecutive or random patient selection	N = 302 Adults <u>Inclusion criteria:</u> • Respiratory symptoms such as dyspnoea, cough or wheezing <u>Exclusion criteria:</u>	<u>Male:Female</u> 127:175 <u>Mean age:</u> Asthma: 46.8 (16.8) Non-asthma: 47.8 (15.6) Medications: Not reported Smokers: Asthma: 36.7% Non-asthma: 21.4%	<u>Index test</u> Questionnaire consisting of 11 questions regarding symptoms within 1 year: Q1 = Have you had wheezing associated with dyspnoea? (score 2) Provoking factors: • Nocturnal aggravation (score 1) • Cold air (score 1) • Exercise (score 1) • Upper respiratory infection (score 1) • Smoke or air pollution (score 1) • Concurrently with coughing (score 1) Q2 = Have you had paroxysmal coughing? (score 1) Q3 = Have you had dyspnoea without wheezing? (score 1) Q4 = Have you had wheezing without dyspnoea? (score 1) Q5 = Have you had fluctuation of	a) only sn/sp values reported, not number of TN, FN, TP and FP. Cut-off ≥3: Sn = 92.4%; Sp = 3.3% Cut-off ≥4: Sn = 85.2%; Sp = 25.0% Cut-off ≥5: Sn = 74.3%; Sp = 47.8% Cut-off ≥6: Sn = 59.5%; Sp = 66.3% Cut-off ≥7: Sn = 40.0%; Sp = 83.7% Cut-off ≥8: Sn = 21.4%; Sp = 89.1% Cut-off ≥9: Sn = 14.3%; Sp = 95.7% Cut-off ≥10: Sn = 8.6%; Sp = 96.7% Cut-off ≥11: Sn = 4.3%; Sp = 98.9% AUC total symptom score: 0.647 (0.033) b) Index test +: Ref std + = 86; Ref std - = 71; Total = 157 Index test -: Ref std + = 124; Ref std - = 21; Total = 145 Total: Ref std + = 210; Ref std - = 92; Total = 302	<u>Source of funding:</u> Korea Asthma Allergy Foundation Research Grant and Korea Health 21 R&D Project, Ministry of Health <u>Limitations:</u> • No drop-outs • Consecutive or random patient selection not mentioned • time between IT and RS unclear but same time

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
	not reported			exacerbation and improvement? (score 2) a) Total symptom score b) Responded yes to Q1 (all provoking factors) c) Responded yes to Q2 d) Responded yes to Q3 e) Responded yes to Q4 f) Responded yes to Q5 Cut-off: various total symptom score cut-off scores reported. ROC analysis of total symptom scores. With an increase in cut-off, sensitivity decreased and specificity increased. Cut-off value of ≥4 associated with highest combination of sn and sp. Even within a total symptom score of ≥4, the sn/sp varied with the combination of symptoms (reported in paper Table 6) <u>Reference standard</u> Physician Dx with objective test (patients with an FEV1 >70% had MCT, all other patients had BDR to short-acting beta2-agonist). Definite Dx of asthma made using test (MCh PC20 <16mg/ml or BDR FEV1 increase >12% and 200ml)	Sensitivity 41.0% Specificity 22.8% PPV / NPV 54.8% / 14.5% c) Ref std + Ref std - Total Index test + 34 53 87 Index test - 176 39 215 Total 210 92 302 Sensitivity 16.2% Specificity 42.4% PPV / NPV 39.1% / 18.1% d) Ref std + Ref std - Total Index test + 24 27 51 Index test - 186 65 251 Total 210 92 302 Sensitivity 11.4% Specificity 70.7% PPV / NPV 47.1% / 25.9% e) Ref std + Ref std - Total Index 18 19 37	suggested <u>Additional data:</u> Symptoms and provoking factors with high prevalence in those Dx with asthma: wheezing with dyspnoea (86%); nocturnal aggrevation (64%); fluctuation (64%); upper respiratory infection (50%); cold air (44%); exercise (40%).

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
					test +				
				Time between index test and reference standard: unclear <u>Target condition</u> Asthma	Index test -	192	73	265	
					Total	210	92	302	
					Sensitivity Specificity		9.0% 79.3%		
					f)	Ref std +	Ref std -	Total	
					Index test +	64	59	123	
					Index test -	146	33	179	
					Total	210	92	302	
					Sensitivity Specificity PPV / NPV		30.5% 35.9% 52.0% / 18.4%		

Table 26: SCHLEICH 2012[1514]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Schleich FN, Asandei R, Manise M, Sele J, Seidel L, Louis R. Is FENO50	<u>Study type:</u> Prospective study <u>Data source:</u> Collected for study	N = 174 <u>Inclusion criteria:</u> Patients referred to chest physicians for methacholine challenge for asthma diagnosis;	<u>Male: Female</u> 72: 102 <u>Mean (SD) age:</u> 41 (16) yrs	<u>Index test</u> Questionnaire concerning symptoms: a) diurnal cough b) nocturnal cough c) diurnal wheezing d) nocturnal wheezing e) dyspnoea	a)	Ref std +	Ref std -	Total	<u>Source of funding:</u> Interuniversity Attraction Poles Project <u>Limitations:</u>
					Index test +	54	68	122	
					Index test -	28	24	52	
					Total	82	92	174	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
useful diagnostic tool in suspected asthma? International Journal of Clinical Practice. 2012; 66(2):158-165. *(Guideline Ref ID SCHLEICH 2012)*	Setting: Department of Pulmonary Medicine Country: Belgium Recruitment: March 13, 2009 to December 30, 2009	bronchodilator test failed to show reversible airway obstruction or baseline spirometry normal Exclusion criteria: Patients already receiving inhaled corticosteroids		Reference standard Methacholine challenge Cut off PC20 <16mg/mL Time between index test and reference standard: same time Target condition Asthma (methacholine challenge positive) vs. methacholine negative FeNO levels: methacholine challenge positive vs. methacholine negative	Sensitivity Specificity PPV / NPV		65.9 26.1 44.3 / 46.2		Additional data: None
					b)	Ref std +	Ref std -	Total	
					Index test +	30	32	62	
					Index test -	52	60	112	
					Total	82	92	174	
					Sensitivity Specificity PPV / NPV		36.6 65.2 48.4 / 53.4		
					c)	Ref std +	Ref std -	Total	
					Index test +	47	35	82	
					Index test -	35	57	92	
					Total	82	92	174	
					Sensitivity Specificity PPV / NPV		57.3 62.0 57.3 / 62.0		
					d)	Ref std +	Ref std -	Total	
					Index test +	46	19	65	
					Index test -	36	73	109	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
					Total	82	92	174	
					Sensitivity Specificity PPV / NPV		56.1 79.3 70.8 / 67.0		
					e)	Ref std +	Ref std -	Total	
					Index test +	60	41	101	
					Index test -	22	51	73	
					Total	82	92	174	
					Sensitivity Specificity PPV / NPV		73.2 55.4 59.4 / 69.9		

Table 27: SCHNEIDER 2009A[1519]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Schneider A et al. 2009. Diagnostic accuracy of spirometry in primary	Study type: Cross-sectional study Setting: Index test in primary care, 14 GPs in 10 practices	N = 219 Adults Inclusion criteria: • Visiting GP for the first time with complaints of suggested obstructive airway disease (OAD).	Male: Female 92:127 Mean (SD) age: 43.8 (15.6) % of symptomatic	Index test: Medical history taken with a structured questionnaire: a) 'Do you sometimes suffer from shortness of breath?' b) 'Have you suffered from wheezing in your chest?' c) 'Do you often suffer from cough?'	a)	Ref st +	Ref st -	Total	Source of funding: Federal ministry of education and research (BMBF), Germany. Limitations:
					Index test +	55	80	135	
					Index test -	35	49	84	
					Total	90	129	219	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
care. BMC Pulmonary Medicine: 9: 31. REF ID: SCHNEIDER2009A	Country: Germany Recruitment: Consecutive recruitment	• Symptoms such as dyspnoea, coughing, or expectoration Exclusion criteria: • Previous Dx for OAD • Previous anti-obstructive medicine • Contraindications for BDR of challenge testing (untreated hyperthyreosis, unstable coronary artery disease, cardiac arrhythmia) • Pregnancy	patients with positive/abnormal spirometry: 35.6% Medications: None prior to spirometry at GP. If necessary, therapy initiated by GP for asthma or COPD but stopped 12 hours prior to lung function lab.	d) 'Do you often suffer from expectoration?' e) 'Have you been woken up with a feeling of tightness in your chest?' f) 'Have you been woken up by an attack of shortness of breath?' Reference standard LUNG FUNCTION LAB: Dx by pneumologist based on whole-body plethysmography (FEV1/VC ≤70% or FEV1 <80%) followed by either BDR if obstruction is present (FEV1 ≥12% and ≥200ml) or methacholine if obstruction is not present (PC20 ≤16mg/ml or extreme increase in airway resistance accompanied by clinical symptoms in two patients) Time between index test and reference standard: unclear Target condition OAD: Asthma or COPD	Sensitivity Specificity PPV/NPV		61.1 38.0 40.7/58.3		Additional data: 3 lost to follow-up
					b)	Ref st +	Ref st -	Total	
					Index test +	47	60	107	
					Index test -	43	69	112	
					Total	90	129	219	
					Sensitivity Specificity PPV/NPV		52.2 53.5 43.9 / 61.6		
					c)	Ref st +	Ref st -	Total	
					Index test +	39	87	126	
					Index test -	51	42	93	
					Total	90	129	219	
					Sensitivity Specificity PPV / NPV		43.3 32.6 31.0 / 45.2		
					d)	Ref st +	Ref st -	Total	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
					Index test +	22	52	74	
					Index test -	68	77	145	
					Total	90	129		
					Sensitivity Specificity PPV/NPV		24.4 59.7 29.7 / 53.1		
					e)	Ref st +	Ref st -	Total	
					Index test +	27	22	49	
					Index test -	63	107	170	
					Total	90	129		
					Sensitivity Specificity PPV/NPV		30.0 82.9 55.1 / 62.9		
					f)	Ref st +	Ref st -	Total	
					Index test +	27	24	51	
					Index test -	63	105	168	
					Total	90	129		
					Sensitivity Specificity		30.0 81.4		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables		Comments
					PPV / NPV	52.9 / 62.5	

Table 28: SCHNEIDER 2012[1517]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
Antonius Schneider, Mehtap Ay, Bernhard Faderl, Klaus Linde, and Stefan Wagenpfeil. Diagnostic accuracy of clinical symptoms in obstructive airway diseases varied within different health care sectors.	Study type: Cross-sectional study Setting: 3 parts /settings: 1. GPs 2. Referral practice (pneumologists) • Hospital (Pts in rehab after long-term respiration, or after weaning from artificial respiration, or pts with severe COPD	N = 778 adults (GP: n=219; pneumologists: n=259; hospital: n=300). Inclusion criteria: **1. GPs:** • first time visit with complaints of suggested OAD or RAD • symptoms for >2 months **2. Pneumologists:** • 1st visit for Dx work-up to include or exclude OAD or RAD • Other criteria as for GPs **3. Hospital** • Pts with suspected OAD who were hospitalised for the	Female GP: 58% Referral: 60% Hospital: 36% Mean age: GP: 43.8 Referral: 46.3 Hospital: 65.3 % of symptomatic patients Dx with asthma: GP: 90 (41%) Referral: 84 (32%) Hospital: 25 (8.3%) Medications: Not mentioned.	Index test: Medical history taken with a structured questionnaire: a) Self-reported wheezing b) Coughing c) Dyspnoea attacks d) Dyspnoea going upstairs e) Dyspnoea when walking f) Dyspnoea on minimal exercise g) Expectoration h) Tightness of chest Reference standard Symptoms + LUNG FUNCTION LAB: Dx by pneumologist based on whole-body plethysmography (FEV1/VC ≤70% or FEV1 <80%) followed by either BDR if obstruction is	**GP (sens/spec)** NOTE: some outcome data was previously reported in Schneider 2009A. a) Self-reported wheezing (52.2 / 53.1) b) Coughing (43.8 / 31.5) c) Dyspnoea attacks (40.0 / 78.4) d) Dyspnoea going upstairs (47.1 / 49.6) e) Dyspnoea when walking (4.8 / 93.2) f) Dyspnoea on minimal exercise (2.5 / 94.1) g) Expectoration (25.3 / 58.7) h) Tightness of chest (31.4 / 82.7) **Pneumologists (sens/spec)** a) Self-reported wheezing (52.4 / 65.6) b) Coughing (52.5 / 63.9) c) Dyspnoea attacks (8.9 / 88.2) d) Dyspnoea going upstairs (54.6 / 40.6) e) Dyspnoea when walking (25.0 / 78.4) f) Dyspnoea on minimal exercise (14.5 / 84.9) g) Expectoration (40.0 / 74.1) h) Tightness of chest (31.7 / 74.7)	Source of funding: Federal ministry of education and research (BMBF), Germany. Limitations: Additional data: None.

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
J.Clin.Epidemiol. 65 (8):846-854, 2012. REF ID: SCHNEIDER2012	needing respiration at home or severe asthma) Country: Germany (multicentre) Recruitment: Consecutive recruitment	first time. Exclusion criteria: **1. GPs:** • Respiratory infections in prior 6 wks • Previous Dx of OAD. **2. Pneumologists:** • As above. **3. Hospital** • None reported.		present (FEV1 ≥12% and ≥200ml) or methacholine if obstruction is not present (PC20 ≤16mg/ml). Most asthma pts were identified by the BPT. Time between index test and reference standard: unclear Target condition OAD: Asthma or COPD	**Hospital (sens/spec)** a) Self-reported wheezing (76.0 / 33.6) b) Coughing (48.0 / 51.8) c) Dyspnoea attacks (32.0 / 81.6) d) Dyspnoea going upstairs (88.0 / 6.7) e) Dyspnoea when walking (36.0 / 32.3) f) Dyspnoea on minimal exercise (32.0 / 42.9) g) Expectoration (41.7 / 51.1) h) Tightness of chest (44.0 / 53.5)	

Table 29: TOMITA 2013[1753]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Tomita et al., 2013. A scoring algorithm for predicting the presence of adult asthma: a prospective	Study type: Cross-sectional study Setting: Outpatient clinic, University Hospital Country: Japan	N = 566 Adults Inclusion criteria: • Adult outpatients with non-specific repiratory symptoms including wheeze, shortness of breath, and cough. Exclusion criteria:	Male: Female 221:345 Median (range) age: 52 years (18-88) Medications: Could be	Index test Five additional questions at routine interview, including: a) 'Have you ever had any experiences of wheezing?' b) 'Did your symptoms occur in the early morning or at night (diurnal variation)?' c) 'Have you had similar episodes of respiratory symptoms (recurrent episodes)?'	a)	Ref st +	Ref st -	Total	Source of funding: None. None of the authors had a financial relationship with a commercial entity Limitations: • Time
					Index test +	110	26	136	
					Index test -	257	173	430	
					Total	367	199	566	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
derivation study. Primary care respiratory journal: 22: 51-58 REF ID: TOMITA2013	<u>Recruitment:</u> All eligible patients between Jan 2008 and Sept 2011 (unclear)	• Abnormal x-ray findings and other causes • Pregnant/ breastfeeding • Current Dx of pneumonia, pneumothorax, atelectasis, pulmonary fibrotic disease, chronic bronchitis, other lower respiratory abnormality. • Systemic or inhaled CS, beta-blockers or angiotensin converting enzyme inhibitors • Symptoms of chest pain or haemosputum.	started on ICS at first visit before MCT	<u>Reference standard</u> Relevant symptom history (all patients) and BDR (FEV1 <200ml and 12%) and/or BHR (methacholine PC20 <8mg/ml) NB. 64/367 patients Dx had clinically Dx asthma (responsive to ICS with neither BDR or BHR) Time between index test and reference standard: within 8 weeks <u>Target condition</u> Asthma	Sensitivity 30.0% Specificity 86.9% PPV / NPV 80.9% / 40.2% b) Ref std + Ref std - Total Index test + 198 62 260 Index test - 169 137 306 Total 367 199 566 Sensitivity 54.0% Specificity 68.8% PPV / NPV 76.2% / 44.8% c) Ref std + Ref std - Total Index test + 107 18 125 Index test - 260 181 441 Total 367 199 566 Sensitivity 29.2% Specificity 91.0%	between tests 8 weeks, but could be started on ICS at first visit • 813 consented but only 566 performed MCT (others declined participation or no AHR) <u>Additional data:</u>

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables		Comments
					PPV / NPV	85.6% / 41.0%	

Table 30: WEVERHESS 1999[1887]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Wever-hess et al., 1999. Prognostic characteristics of asthma diagnosis in early childhood in clinical practice. Acta Paediatrica: 88: 827-834. REF ID: WEVERHESS1999	<u>Study type:</u> Longitudinal prognostic study <u>Setting:</u> Outpatient department, Children's Hospital <u>Country:</u> Netherlands <u>Recruitment:</u> All children from Jan 1991 to Jan 1993	N = 188 (including aged 2-4yr subgroup only) <u>Inclusion criteria:</u> Aged 0-4 years with symptoms that were suggestive of asthma <u>Exclusion criteria:</u> Symptoms that could be explained by other respiratory disorders, such as respiratory syncytial virus bronchiolitis, cystic fibrosis, gastro-oesophageal reflux	<u>Male: Female</u> 108:80 <u>Mean (SD) age:</u> 37 (8.4) months Medications at initial visit: Beta-agonists 42%, deptropine 10%, anticholinergics 3%, antihistamines 20%, anti-inflammatory 5%, antibiotics 49%.	<u>Index test</u> Symptoms (visit and questionnaire): a) cough b) wheeze c) cough and wheeze d) shortness of breath <u>Reference standard</u> Dx taken from medical notes at follow-up (2 years later). Dx made by a paediatrician on clinical grounds, based on recurrence of symptoms and need for and response to therapy according to the guidelines for diagnosis of asthma in young children (follow up statement from the International Paediatric Asthma Consensus Group).	a)	Ref st +	Ref st -	Total	<u>Source of funding:</u> Supported financially by Stichting Astmabestrijding, Amsterdam <u>Limitations:</u> Follow up at 2 years, prognostic design <u>Additional data:</u> Data provided from children aged 0-1 year separately but does not match protocol.
					Index test +	127	41	168	
					Index test -	17	3	20	
					Total	144	44	188	
					Sens / Spec PPV / NPV		88.2% / 6.8% 75.6% / 15.0%		
					b)	Ref std +	Ref std -	Total	
					Index test +	78	19	97	
					Index test -	66	25	91	
					Total	144	44	188	
					Sens / Spec PPV / NPV		54.2% / 56.8% 80.4% / 27.5%		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
				<u>Time between index test and reference standard:</u> 2 years <u>Target condition</u>	c)	Ref std +	Ref std -	Total	
					Index test +	70	18	88	
					Index test -	74	26	100	
					Total	144	44	188	
					Sens / Spec PPV / NPV		48.6% / 59.1% 79.5% / 26.0%		
					d)	Ref std +	Ref std -	Total	
					Index test +	109	21	130	
					Index test -	35	23	58	
					Total	144	44	188	
					Sens / Spec PPV / NPV		75.7% / 52.3% 83.8% / 39.7%		
					PROGNOSTIC DATA (multivariate): **Predictors of Asthma Dx 2 years later (n=188)** • Shortness of breath was a prognostic factor (OR 3.10, 95% CI 1.49-6.47) • Wheeze was not a prognostic factor				

G.2 History of atopic disorders

Table 31: CORDIERO 2011[360]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Cordiero et al., 2011. Utility of nitric oxide for the diagnosis of asthma in an allergy clinic populatio n. Allergy and Asthma Proceedin gs: 32: 119-126. REF ID: CORDIERO 2011	Study type: Cross-sectional observationa l study Setting: General outpatient allergy clinic Country: The Netherlands Recruitment: All from January 2007 to September 2007	N = 114 Adults and children/young people Inclusion criteria: • New referrals to outpatient allergy clinic • Symptoms of nasal or ocular complaints; pulmonary complaints; skin complaints and general complaints. Exclusion criteria: • Patients using inhaled corticosteroids or oral corticosteroids within 6 weeks	Male: Female 43:71 Median (range) age: 38.5 (7-87) Medications: Treatment with short acting bronchodilators allowed up to 8 hours before and long acting bronchodilators and antihistamines up to 48 hours before.	Index test Family history (unclear if first degree relatives and if history of asthma or atopy) Reference standard History of typical respiratory symptoms and FEV1 improvement >12% and >200mL with salbutamol 400µg or PC20 histamine ≤8mg/mL according to GINA. Time between index test and reference standard: 6 weeks Target condition Asthma diagnosis vs. non-asthma (Allergic rhinitis, non-allergic rhinitis, eczema, urticarial, other analysed all together)		Ref st +	Ref st -	Total	Source of funding: Not stated Limitations: • Family history (unclear if first degree relatives and if history of asthma or atopy). Additional data:
					Index test +	25	32	57	
					Index test -	17	40	57	
					Total	42	72	114	
					Sensitivity Specificity PPV NPV		59.5% 55.6% 43.9% 70.2%		

Table 32: DEILAMI 2009[408]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Deilami et al., 2009. Evaluation of methacholine challenge test results in chronic cough patients referring to clinic of pulmonary disease. Acta Medica Iranica: 47: 175-179. REF ID: DEILAMI2009	Study type: Cross sectional study Setting: Hospital pulmonary disease clinic Country: Iran Recruitment: All patients who were not excluded (unclear)	N = 81 Inclusion criteria: • Suffering from cough for at least 8 weeks and went to the pulmonary disease clinic. • Normal spirometry Exclusion criteria: • Patients with PND • Patients of GERD who were untreated • Respiratory infection within the last 3 weeks or contraindication to methacholine.	Male: Female 45:36 Mean age: 32.5 (13.1) Medications: n=7 smokers	Index test Personal history of allergy NB Family history of asthma sens/spec data was not extracted as was not first class relatives only Reference standard Methacholine challenge test: concentrations of 0.03, 0.06, 0.125, 0.25, 0.5, 1, 2, 4, 8 and 16mg/ml, until FEV1 drop of 20% or more. Cut-off: PC20 ≤4mg/ml Time between index test and reference standard: Target condition Asthma		Ref st +	Ref st -	Total	Source of funding: Not reported Limitations: • • Additional data:
					Index test +	13	15	28	
					Index test -	11	42	53	
					Total	24	57	80	
					Sensitivity Specificity PPV NPV		54.2% 73.7% 46.4% 20.8%		

Table 33: TOMITA 2013[1753]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Tomita et al., 2013. A scoring algorithm for predicting the presence of adult asthma: a prospective derivation study. Primary care respiratory journal: 22: 51-58 REF ID: TOMITA2013	Study type: Cross-sectional study Setting: Outpatient clinic, University Hospital Country: Japan Recruitment: All eligible patients between Jan 2008 and Sept 2011 (unclear)	N = 566 Adults Inclusion criteria: • Adult outpatients with non-specific respiratory symptoms including wheeze, shortness of breath, and cough. Exclusion criteria: • Abnormal x-ray findings and other causes • Pregnant/ breastfeeding • Current Dx of pneumonia, pneumothorax, atelectasis, pulmonary fibrotic disease, chronic bronchitis, other lower respiratory abnormality. • Systemic or inhaled CS, beta-blockers or angiotensin converting enzyme inhibitors • Symptoms of chest pain or	Male: Female 221:345 Median (range) age: 52 years (18-88) Medications: Could be started on ICS at first visit before MCT	Index test Routine interview including following questions: a) Personal history: 'Have you had any medical history of allergic diseases such as asthma, atopic dermatitis, and allergic rhinitis?' b) Family history: 'Do you have any close relatives with allergic disease?' Reference standard Relevant symptom history (all patients) and BDR (FEV1 <200ml and 12%) and/or BHR (methacholine PC20 <8mg/ml) NB. 64/367 patients Dx had clinically Dx asthma (responsive to ICS with neither BDR or BHR) Time between index test and reference standard: within 8 weeks Target condition Asthma	a)	Ref st +	Ref st -	Total	Source of funding: None. None of the authors had a financial relationship with a commercial entity Limitations: • Time between tests 8 weeks, but could be started on ICS at first visit • 813 consented but only 566 performed MCT (others declined participation or no AHR) Additional data:
					Index test +	202	64	266	
					Index test -	165	135	300	
					Total	367	199	566	
					Sensitivity Specificity PPV NPV		55.0% 67.8% 75.9% 45.0%		
					b)	Ref std +	Ref std -	Total	
					Index test +	95	34	129	
					Index test -	272	165	437	
					Total	367	199	566	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables		Comments
		haemosputum.			Sensitivity Specificity PPV NPV	25.9% 82.9% 73.6% 37.8%	

Table 34: WEVERHESS 1999[1887]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Wever-hess et al., 1999. Prognostic characteri stics of asthma diagnosis in early childhood in clinical practice.	Study type: Longitudinal prognostic study Setting: Outpatient department, Children's Hospital Country: Netherlands	N = 188 (including aged 2-4yr subgroup only) Inclusion criteria: • Aged 0-4 years with symptoms that were suggestive of asthma Exclusion criteria:	Male: Female 108:80 Mean (SD) age: 37 (8.4) months Medications at initial visit: Beta-agonists 42%,	Index test History taken at initial visit: a) Past or present rhinitis b) past or present eczema c) family history Reference standard Dx taken from medical notes at follow-up (2 years later). Dx made by a paediatrician on clinical	a)	Ref st +	Ref st -	Total	Source of funding: Supported financially by Stichting Astmabestrijding, Amsterdam Limitations:
					Index test +	89	35	124	
					Index test -	55	9	64	
					Total	144	44	188	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Acta Paediatrica: 88: 827-834. REF ID: WEVERHESS1999	<u>Recruitment:</u> All children from Jan 1991 to Jan 1993	• Symptoms that could be explained by other respiratory disorders, such as respiratory syncytial virus bronchiolitis, cystic fibrosis, gastro-oesophageal reflux	deptropine 10%, anticholinergics 3%, antihistamines 20%, anti-inflammatory 5%, antibiotics 49%.	grounds, based on recurrence of symptoms and need for and response to therapy according to the guidelines for diagnosis of asthma in young children (follow up statement from the International Paediatric Asthma Consensus Group). Time between index test and reference standard: 2 years <u>Target condition</u>	Sensitivity Specificity PPV NPV		61.8% 20.5% 71.8% 14.1%		<u>Additional data:</u> Data provided from children aged 0-1 year separately but does not match protocol.
					b)	Ref std +	Ref std -	Total	
					Index test +	67	11	78	
					Index test -	77	33	110	
					Total	144	44	188	
					Sensitivity Specificity PPV NPV		46.5% 75.0% 85.9% 30.0%		
					c)	Ref std +	Ref std -	Total	
					Index test +	63	19	82	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
					Index test -	81	25	106	
					Total	144	44	188	
					Sensitivity Specificity PPV NPV		43.8% 56.8% 76.8% 23.6%		

Table 35: VANDERMARK 2014[1802]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Predicting asthma in preschool children at high risk presenting in primary care: development of a clinical asthma prediction score.	Study type: Longitudinal prognostic study (demographic data and clinical history obtained from questionnaire. Sensitivity and specificity calculated from for Dx	N = 771 (438 had information for diagnosis at age 6 years) Inclusion criteria: Aged 1-5 years. Presented in primary care in the previous 12 months with current coughing (≥2 visits), wheezing (≥1 visits), and/or shortness of breath (≥1 visits) (only those	Male: Female 249:189 Mean (SD) age: At baseline for study: 3.0 (1.3). Note: diagnosis made at aged 6 years Medications: unclear	Index test Questionnaire administered at baseline and at 6 years: a) Family history of asthma (parents and/or siblings) Reference standard At age 6 years, spirometry and BHR obtained in children with wheezing, shortness of breath, recurrent coughing or use of asthma medication during the previous 12	a)	Ref st +	Ref st -	Total	Source of funding: Not reported Limitations: Additional data:
					Index test +	80	76	156	
					Index test -	107	175	282	
					Total	187	251	438	
					Sens Spec		43.8% 69.7%		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
Primary Care Respiratory Journal. 2014; 68(1):52-59. REF ID: VANDERMARK2014	at 6 years of age) <u>Setting:</u> Primary care <u>Country:</u> Netherlands <u>Recruitment:</u> Children participating in the ARCADE prospective cohort study	with symptoms in the past year included in asthma Dx at age 6 years). <u>Exclusion criteria:</u>		months. Dx defined as having persistent symptoms and/or using asthma medication in the last year in combination with BHR (methacholine <8mg.ml) or BDR (>10% increase in FEV1). <u>Time between index test and reference standard:</u> Unclear if index test (clinical history) was taken at baseline or at 6 years. <u>Target condition</u> Asthma		

G.3 Symptoms after exercise

Table 36: Choi 2007[315]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Choi et al., 2007. Easy diagnosis of asthma: computer-assisted, symptom-based diagnosis. Journal of Korean Medical Science: 22: 832-838. REF ID: CHOI2007	Study type: Diagnostic cross sectional study Setting: Hospital outpatient dept. Country: Korea Recruitment: Consecutive or random patient selection not reported	N = 302 Adults Inclusion criteria: • Respiratory symptoms such as dyspnoea, cough or wheezing Exclusion criteria:	Male:Female 127:175 Mean age: Asthma: 46.8 (16.8) Non-asthma: 47.8 (15.6) Medications: Not reported Smokers: Asthma: 36.7% Non-asthma: 21.4%	Index test Questionnaire consisting of 11 questions regarding symptoms. Q3 = Have you had wheezing associated with dyspnoea (provoking factor – exercise)? Cut-off: affirmative answer to Q3 Comparator test n/a Reference standard Physician Dx with objective test (patients with an FEV1 >70% had MCT, all other patients had BDR to short-acting beta2-agonist). Definite Dx of asthma made using test (MCh PC20 <16mg/ml or BDR FEV1 increase >12% and 200ml) Time between index test and reference standard: unclear		Ref std +	Ref std -	Total	Source of funding: Korea Asthma Allergy Foundation Research Grant and Korea Health 21 R&D Project, Ministry of Health Limitations: • No drop-outs • Consecutive or random patient selection not mentioned • time between IT and RS unclear but same time suggested Additional data:
					Index test +	84	20	104	
					Index test -	126	72	198	
					Total	210	92	302	
					Sensitivity Specificity PPV NPV		40.0% 78.3% 80.8% 36.4%		
						Ref std +	Ref std -	Total	
					Index test +				

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
				Target condition Asthma	Index test -				
					Total				
					Sensitivity Specificity PPV NPV				

G.4 Occupational asthma

Table 37: BAUR 1998[130]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Baur X et al. Relation between occupatio	Study type: Diagnostic Cross-sectional study	N = 62 healthcare workers (airborne latex; 12 asthma)	Male: Female Not stated Mean age:	Index test Asking whether their symptoms are better away from work	**Occupational asthma: health care workers (latex)**	Ref std +	Ref std –	Total	Source of funding: None stated

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
nal asthma case history, bronchial methacholine challenge, and specific challenge test in patients with suspected occupational asthma. Am J Industr Med 1998; 33: 114-122. BAUR1998	<u>Data source:</u> Industrial medicine institute <u>Setting:</u> Symptomatic <u>Country:</u> Germany <u>Recruitment:</u> 1992 to 1997	28 bakers (flour, baking enzymes; 7 asthma) 114 isocyanate workers (isocyanates; 21 asthma) <u>Inclusion criteria:</u> Healthcare workers with contact with latex gloves, bakers or isocyanate workers presenting with suspected occupational asthma <u>Exclusion criteria:</u> Challenge tests contraindicated or declined	Healthcare workers 31 (8.1); bakers 32 (11.9); isocyanate workers 39 (11.1) years	**CUT-OFF:** positive = Reversible airways narrowing (SOB, wheeze) causally related to exposure in the working environment occurred repeatedly <u>Reference standard</u> **Clinical Dx** including objective test: Specific conductance (sG_{aw}) dropped ≥40% from baseline and absolute value $\leq 0.5(kPa*s)^{-1}$ Time between index test and reference standard: same time <u>Target condition</u> Occupational asthma	Question +	11	34	45	<u>Limitations:</u> <u>Additional data:</u> Sensitivity etc calculated
					Question -	1	16	17	
					Total	12	50	62	
					Sensitivity Specificity		92% 32%		
					PPV NPV		24% 94%		
					Occupational asthma: bakers (flour/enzyme)	Ref std +	Ref std –	Total	
					Question +	7	8	15	
					Question -	0	13	13	
					Total	7	21	28	
					Sensitivity Specificity		100% 62%		
					PPV NPV		47% 100%		
					Occupational asthma: isocyanate workers	Ref std +	Ref std –	Total	
					Question	14	32	46	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
					+				
					Question -	7	61	68	
					Total	21	93	114	
					Sensitivity Specificity		67% 66%		
					PPV NPV		30% 90%		

Table 38: Malo 1991[1067]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Malo J-L et al. Is the clinical history a satisfactory means of diagnosing occupational asthma? Am Rev Respir Dis 1991; 143: 528-532.	Study type: Diagnostic Cross-sectional study Data source: Chest clinic Setting: Symptomatic Country: Canada	N = 162 Inclusion criteria: Consecutive cases referred for possible occupational asthma Exclusion criteria: None given	Male: Female 125:37 Mean age: 39.6 (11.8) years	Index test Asking whether their symptoms are better away from work **CUT-OFF:** positive = Whether symptoms worse during or after work and improved during weekends and holidays – history "very likely" or "likely" Reference standard **Clinical Dx** including objective test: Final diagnosis including specific inhalation challenges, serial monitoring of peak flow at work and away from work or both. Fall in FEV1 > 20% (or ≥15% in late component of dual reactions) on specific challenge	**Occupational asthma**	Ref std +	Ref std –	Total	Source of funding: Not stated Limitations: Additional data: PPV and NPV reported; sensitivity and specificity calculated
					Question +	65	39	104	
					Question -	10	48	58	
					Total	75	87	162	
					Sensitivity Specificity		87% 55%		
					PPV NPV		63% 83%		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
MALO 1991	Recruitment: 1987 to 1989			or patterns suggestive of work-related asthma using graphs of individual, mean, maximum and minimum daily values using Burge criteria Time between index test and reference standard: same time Target condition Occupational asthma (isocyanates, flour, grain dust, red and white cedar, pharmaceutical products, sawmills, laboratory animals)			

Table 39: Vandenplas 2001[1821]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Vandenplas O et al. Occupational asthma in symptomatic workers exposed to natural rubber latex:	Study type: Diagnostic Cross-sectional study Data source: Chest clinic Setting: Symptomatic	N = 45 Inclusion criteria: Consecutive patients referred for investigation of possible OA caused by latex; exposed at work to airborne natural rubber latex (NRL) allergens from NRL gloves.	Male: Female 2:43 Mean age: 33.6 years	Index test Asking whether their symptoms are better away from work **CUT-OFF:** positive = Symptoms present only on work days Reference standard **Clinical Dx** including objective test: SICs with NRL gloves; FEV1 fell by more than 20%	**Occupational asthma (latex)**	Ref std +	Ref std –	Total	Source of funding: Programme d'appui scientifique à la protection des travailleurs, Services fédéraux des affaires scientifiques, techniques et
					Question +	15	4	19	
					Question -	16	10	26	
					Total	31	14	45	
					Sensitivity Specificity		48% 71%		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Evaluation of diagnostic procedures. J Allergy Clin Immunol 2001; 107(3): 542-547. VANDENPLAS 2001	Country: Belgium Recruitment: 1993 to 1998	Exclusion criteria: None given		Time between index test and reference standard: same time Target condition Occupational asthma (latex)	PPV NPV	79% 38%	culturelles Limitations: Additional data: Sensitivity and specificity etc calculated

Table 40: Vandenplas 2005[1821]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
What are the questionnaire items most useful in identifying subjects with occupational asthma? European Respirator	Study type: Diagnostic Cross-sectional study Data source: Chest clinic Setting: Symptomatic	N = 212 Inclusion criteria: Prospectively assessed in outpatient clinics of four hospital centres and who underwent objective testing with specific inhalation challenges.	Male: Female 125:87 Mean age: 38.8 (10.7) years	Index test: Asking whether their symptoms are better away from work • **CUT-OFF:** positive = a) Improvement or disappearance of symptoms at weekends • b) Improvement or disappearance of symptoms during vacations Reference standard **Clinical Dx**	**Occupational asthma – Question a**	Ref std +	Ref std –	Total	Source of funding: Actions de Recherche Concertées, Communauté Française de Belgique, Belgium.
					Question +	55	64	119	
					Question -	17	76	93	
					Total	72	140	212	
					Sensitivity Specificity		76% 54%		Limitations:

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
y Journal. 2005; 26(6):1056-1063 VANDENPLAS 2005	Country: Belgium, Canada, Italy, Spain Recruitment: not stated	Exclusion criteria: None given		including objective test: specific inhalation challenge; a sustained fall in forced expiratory volume in one second of 20% Time between index test and reference standard: same time Target condition Occupational asthma (flour and cereals, latex, isocyanates, other chemicals, wood dust, laboratory animals, persulfate, resins and glues, various proteins, metals)	PPV NPV		41% 80%		Additional data: Sensitivity and specificity etc reported; raw data calculated
					Occupational asthma – question b	Ref std +	Ref std –	Total	
					Question +	53	60	113	
					Question -	19	80	99	
					Total	72	140	212	
					Sensitivity Specificity		74% 57%		
					PPV question NPV		57% 74%		

G.5 Spirometry/flow volume loop measures

Table 41: FORTUNA 2007[505]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Fortuna et al., 2007. Diagnostic utility of inflammatory	Study type: Cross sectional study Setting: Referred to	N = 50 Adults Inclusion criteria: • Referred with a clinical history suggestive of	Male: Female 21:29 Age range: 18-68	Index test Spirometry was performed following international guidelines with a Datospir 120 (Sibelmed, Barcelona, Spain). A FEV1 ≥80% of predicted and/or a ratio of		Ref st +	Ref st -	Total	Source of funding: Not reported Limitations: • RS objective MCT is
					Index test +	5	0	5	
					Index test -	17	22	39	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
biomarkers in asthma: exhaled nitric oxide and induced sputum eosinophil count. Respiratory Medicine: 101: 2416-2421 REF ID: FORTUNA	hospital based outpatient clinic Country: Spain Recruitment: Consecutive	asthma (dry cough, wheezing, and shortness of breath) Exclusion criteria: • Conditions that could affect FENO or Eos% measurement for reasons other than asthma: subjects with symptoms of respiratory tract infection in the previous 6 weeks or with systemic manifestations of atopy (rash, digestive	% of symptomatic patients with positive/abnormal spirometry (FEV1/FVC<75% or FEV1 <80%): 10% Medications: no CS within the last 4 weeks	FEV1/FVC ≥75% were considered to lie within normal limits. Cut-off: Obstruction: FEV1 <80% Comparator test n/a Reference standard Methacholine challenge test (PD20 ≤16mg/ml) following guidelines of the GINA Time between index test and reference standard: 1 day	Total	22	22	44	16mg/ml • Unclear why 6 patients not included in analysis of sn/sp • Suggests IT is FEV1<80% and unclear if also includes FEV1/FVC Additional data: 7 of original 57 patients excluded as on CS treatment 6 out of the 50
					Sensitivity Specificity PPV NPV AUC FEV1/FVC		22.7% 100% 100% 56.4% 0.64 (95% CI, 0.49–0.77; p<0.008) 0.63 (95% CI, 0.48–0.76; p<0.006)		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
2007		symptoms, etc.) • Received treatment with inhaled or oral corticosteroids in the last 4 weeks		Target condition Asthma		patients not included in analysis of sn/sp for spirometry and not mentioned

Table 42: PINO 1996[1351]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Pino et al., 1996.	Study type: Cross-	N = 84 Adults	Male: Female 53:31	Index test Spirometry: Pneumoscreen II		Ref st + 	Ref st - 	Total 	Source of funding:

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Value of the peak expiratory flow in bronchodynamic tests. Allergologia et Immunopathologia: 24: 54-57 REF ID: PINO1996	sectional study Setting: University hospital Country: Spain Recruitment: Not stated	Inclusion criteria: • Clinically suspected of bronchial asthma Exclusion criteria: • Worsening of symptoms in the preceding 2 months • A respiratory infection in the lower or upper tract in the preceding 6 weeks • Vaccination with live attenuated virus 6 weeks prior to the test • The existence of a recurrent pathology • Cases of whistling in observed in pulmonary auscultation were excluded from the bronchial provocation test.	Mean age: 46.5 (13.7) Medications: Smoking prohibited 2 hours before the study; discontinuation 48 hours in advance of beta-agonists; theophyllines; anticholinergics; antihistamines; nedochromil; chromoglicate.	(Jagger) according to ATS criteria Cut-off: FEV1/FVC<70% and FEV1<80% Comparator test n/a Reference standard If obstructive spirometry: performed BDR (400µg salbutamol; FEV1 >15% initial) If normal spirometry: methacholine challenge test five breaths of 5mg/ml and five breaths of 25mg/ml, test positive if a 20% drop in FEV1 Time between index test and reference standard: Target condition	Index test +	20	24	44	Not reported Limitations: • Unclear of the directness of the population as few details reported • Unclear time between RS and IT • Random or consecutive recruitment not reported • Patients have different RS objective tests depending on if they were negative or positive to IT • Unclear if suitable cut-off used for MCT Additional data:
					Index test -	23	17	40	
					Total	43	41	84	
					Sensitivity Specificity PPV NPV		46.5% 41.5% 45.5% 42.5%		
						Ref std +	Ref std -	Total	
					Index test +				
					Index test -				
					Total				

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables		Comments
					Sensitivity Specificity PPV NPV		

Table 43: POPOVIC 2012[1367]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Popovic-Grle et al., 2002. Clinical validation of bronchial hyperresponsiveness, allergy tests and lung	<u>Study type:</u> Cross-sectional study <u>Setting:</u> Outpatient department, University Hospital <u>Country:</u> Croatia	N = 195 Adults <u>Inclusion criteria:</u> • Referred by GP with suspected asthma and symptoms of breathlessness / dyspnoea. <u>Exclusion criteria:</u> • Serious diseases of	<u>Male, %</u> 51% of those given an asthma Dx <u>Mean age:</u> 36.5 (6.2) in those given an asthma Dx (n=141)	<u>Index test</u> Spirometry: measured at least 3 times by forced expiration on Vitalograph apparatus with a pneumotachograph. Best attempt recorded. Cut-off: FEV1 <80% predicted <u>Comparator test</u> n/a		Ref st +	Ref st -	Total	<u>Source of funding:</u> Not reported <u>Limitations:</u> • Details of reference standard objective test not given • Unclear if RS results
					Index test +	63	37	100	
					Index test -	78	17	95	
					Total	141	54	195	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
function in the diagnosis of asthma in persons with dyspnoea. Collegium Antropologicum: 26 Suppl: 119-127 REF ID: POPOVIC 2002	<u>Recruitment:</u> Random	other organ systems or the lungs (apart from those of an obstructive and/or allergic nature)	Medications: Not reported	<u>Reference standard</u> Dx made on the basis of questionnaire, with typical medical history data of occasional asthma attacks with wheezing and nocturnal awakening because of dyspnoea, and reversible bronchial obstruction after salbutamol test (no further details stated) Time between index test and reference standard: same time <u>Target condition</u> Asthma	Sensitivity Specificity PPV NPV	44.7% 31.5%			interpreted without knowledge of the IT results • Unclear if IT results interpreted without knowledge of the RS results (but objective) <u>Additional data:</u>

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments

Table 44: SCHNEIDER 2009A[1519]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables			Comments
Schneider A et al. 2009. Diagnostic accuracy of spirometry in primary care. BMC Pulmonary Medicine: 9: 31. REF ID: SCHNEIDER2009A	Study type: Cross-sectional study Setting: Index test in primary care, 14 GPs in 10 practices Country: Germany Recruitment: Consecutive recruitment	N = 219 Adults Inclusion criteria: • Visiting GP for the first time with complaints of suggested obstructive airway disease (OAD). • Symptoms such as dyspnoea, coughing, or expectoration Exclusion criteria: • Previous Dx for OAD • Previous anti-obstructive medicine • Contraindications	Male: Female 92:127 Mean (SD) age: 43.8 (15.6) % of symptomatic patients with positive/abnormal spirometry: 35.6% Medications: None prior to spirometry at GP. If necessary, therapy initiated by GP for asthma or	Index test: Spirometry at GP Electronic spirometer (Medikro Spirostar USB). Best of 3 consecutive spirometric values used in accordance with European Respiratory Society (ERS). Max inspiratory and expiratory flow volume curves generated by forced deep inspiration and expiration with intervening periods of tidal breathing. Cut-off: OAD if FEV1/VC ≤70% and/or FEV1 <80% Comparator test None Reference standard LUNG FUNCTION LAB: Dx by		Ref st +	Ref st -	Total	Source of funding: Federal ministry of education and research (BMBF), Germany. Limitations: • Spirometry performed with full adherence to ERS guidelines in 39.8% of cases and moderate adherence in 38% of cases. ERS criteria
					Index test +	26	52	78	
					Index test -	63	75	138	
					Total	89	127	216	
					Sensitivity Specificity PPV NPV		29.2% 59.1% 33.3% 54.3%		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
		for BDR of challenge testing (untreated hyperthyreosis, unstable coronary artery disease, cardiac arrhythmia) • Pregnancy	COPD but stopped 12 hours prior to lung function lab.	pneumologist based on whole-body plethysmography (FEV1/VC ≤70% or FEV1 <80%) followed by either BDR if obstruction is present (FEV1 ≥12% and ≥200ml) or methacholine if obstruction is not present (PC20 ≤16mg/ml or extreme increase in airway resistance accompanied by clinical symptoms in two patients) Time between index test and reference standard: unclear <u>Target condition</u> OAD: Asthma or COPD		not fulfilled in 22.2% of cases. • Unclear time between IT and RS; 74 patients from original 293 only wanted the IT and did not have RS • RS objective MCT is 16mg/ml <u>Additional data:</u> 3 lost to follow-up Gives sn/sp of spirometry for asthma and COPD separately (data combined here to include all patients presenting with respiratory symptoms regardless of their final Dx)

Table 45: SIVAN 2009[1602]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Sivan et al., 2009. The use of exhaled nitric oxide in the diagnosis of asthma in school children. Journal of Pediatrics: 155: 211-216 REF ID: SIVAN2009	Study type: Cross-sectional study Setting: Outpatient paediatric pulmonary clinic, Children's Hospital Country: Israel Recruitment: Consecutive	N = 150 (113 excluding those on ICS from analysis) Children Inclusion criteria: • Non-specific respiratory symptoms suggestive of asthma for at least 3 months, including cough, wheezing and shortness of breath with or without trials of treatment with bronchodilators and ICS. • Follow-up for at least 1 year Exclusion criteria: • Symptoms of unresolved respiratory tract infection • Systemic clinical manifestations of atopy such as anaphylaxis, angioedema, food allergy, urticarial, systemic or inflammatory disease	Male: Female ~56% male Age range: 5-18yrs (mean 12) Medications: Withheld bronchodilators for 24 hours. Unclear if on medications for 18 months between IT and RS.	Index test Spirometry: hand-held spirometer (Micro-lab ML3500/S, Micro-Medical, UK). Cut-off: FEV1 <80% Reference standard Made by paediatric pulmonologist after 18 months follow-up. Based on history of 2 or more clinical exacerbations of wheezing documented by a physician; dyspnoea or cough relived by bronchodilators; documented variability in FEV1 ≥15% in response to bronchodilators at any time during the follow-up period; OR documented variability in FEV1 ≥15% over time with or without controller medications (ICS or montelukast). Results of provocation tests included when available. Time between index test and reference standard: 18 months		Ref st +	Ref st -	Total	Source of funding: Not reported Limitations: • Recruited 150 patients but excluded 37 on ICS from analysis • Time between IT and RS = 18 months • Unclear if all had objective test with RS • Interpretation of RS not done blinded to results of spirometry IT Additional data:
					Index test +	36	12	48	
					Index test -	33	32	65	
					Total	69	44	113	
					Sensitivity Specificity PPV NPV		52% 72% 75% 48%		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
				Target condition Asthma					

Table 46: SMITH 2004[1613]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Smith et al., 2004. Clinical usefulness of fractional exhaled nitric	Study type: Cross-sectional study Setting: Referred to hospital pulmonary	N = 47 Adults and children (8-75 years) Inclusion criteria: • Referred to hospital pulmonary function lab by GP for possible asthma	Male: Female Mean age: Medications:	Index test Spirometry Cut-off: FEV1 <90% predicted FEV1 <80% predicted FEV1/FVC <80%	**FEV1/FVC <70%**	Ref st +	Ref st -	Total	Source of funding: Supported by Otago Medical Research Foundation and the Otago respiratory
					Index test +	6	0	6	
					Index test -	11	30	41	
					Total	17	30	47	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
oxide for diagnosing prolonged cough. Respiratory Medicine: 102: 1452-1459. REF ID: SMITH2004	function lab Country: New Zealand Recruitment: Consecutive	• Respiratory symptoms for a minimum of 6 weeks Exclusion criteria: • Used ICS in the preceding 4 weeks • Typical respiratory tract infection in the preceding 6 weeks	Short-acting beta-agonists and anticholinergic inhalers permitted during the study period but withheld for a minimum of 6 hours before the study visit.	FEV1/FVC <70% Comparator test n/a Reference standard Relevant symptom history (all patients) and a positive hypertonic saline challenge test (PD15<20ml) or BDR increase in FEV1 ≥12% Time between index test and reference standard: 2 weeks Target condition Asthma	Sensitivity 35.3% Specificity 100% PPV 100% NPV 73.2% AUC FEV1/FVC 0.678 **FEV1/FVC <80%** / Ref st + / Ref st - / Total Index test + 8 / 6 / 14 Index test - 9 / 24 / 33 Total 17 / 30 / 47 Sensitivity 47.1% Specificity 80.0% PPV 57.1% NPV 72.7% **FEV1 <80% pred** / Ref st + / Ref st - / Total Index test + 5 / 0 / 5 Index test - 12 / 30 / 42 Total 17 / 30 / 47 Sensitivity 29.4% Specificity 100% PPV 100% NPV 72.4%	research trust. GSK personal education grant to one author. Limitations: • • Additional data: 4 of the original 51 patients withdrew after first study visit due to time commitments.

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
					AUC FEV1%pred		0.804		
					FEV1 <90% pred	Ref st +	Ref st -	Total	
					Index test +	6	2	8	
					Index test -	11	28	39	
					Total	17	30	47	
					Sensitivity		35.3%		
					Specificity		93.3%		
					PPV		75%%		
					NPV		71.8%		

G.6 Bronchodilator reversibility

Table 47: BRAND 1992[213]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Brand PLP et al. Interpretation of bronchodilator response	Study type:Diagnostic cross-sectional study	N = 150 Inclusion criteria: • Adults with chronic respiratory symptoms (asthma	Male: Female Not stated Mean age: 18-60 years; mean not stated	Index testBronchodilator reversibility: Response to inhaled terbutaline 1000µg a) change [Δ]FEV1 % init; b) ΔFEV1[l] i.e. absolute value in litres; c) ΔFEV1 % init and ΔFEV1[l]; d) ΔFEV1 %pred; e) standardised residual [SR]-FEV1;	**Asthma**	Ref std +	Ref std –	Total	Source of funding: Not stated Limitations: Some
					Bronchodilator reversibility	68	24	92	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
in patients with obstructive airways disease. Thorax 1992; 47: 429-436. BRAND1992	<u>Data source:</u> University hospital outpatients departments <u>Setting:</u> Secondary care <u>Country:</u> The Netherlands <u>Recruitment:</u> Not stated.	or COPD) in university hospital outpatients departments; baseline FEV1 >1.2 litres and 1.64-4.5 residual standard deviations below predicted value, or FEV1/inspiratory vital capacity ratio >1.64 RSD below predicted; hyperresponsive to inhaled histamine <u>Exclusion criteria:</u> Pregnant women; history of occupational asthma or other serious diseases (e.g. TB, MI, malignancy); oral corticosteroids, beta-blockers, nitrates or anticoagulants; continuous antibiotics.	Tx was withdrawn for 14days and BD Tx for 12 days.	f) FEV1 post-bronchodilator [pb] %pred **CUT-OFF:** positive = a) ΔFEV1 % init >15%; b) ΔFEV1[l] > 0.200; **c) ΔFEV1 % init >15% and ΔFEV1[l] > 0.200;** d) ΔFEV1 %pred >9%; e) SR-FEV1 > 0.5; f) FEV1 pb %pred >80% <u>Reference standard</u>**Clinical Dx** Standardised history using criteria of American Thoracic Society: asthma = attacks of breathlessness and wheeze (asthma attacks) without chronic (>3 months/year) cough or sputum production; COPD = Current or former smokers without a history of asthma attacks reporting either chronic cough +/- sputum production, or dyspnoea when walking quietly on level ground, or both Plus hyper-responsiveness to inhaled histamine Time between index test and reference standard: same time <u>Target condition</u> Asthma	(a) +				exclusions may limit generalisability <u>Additional data:</u> Raw data not stated; calculated from sensitivity and specificity
					Bronchodilator reversibility (a) -	31	27	58	
					Total	99	51	150	
					Sensitivity (a)		68.7%		
					Specificity (a)		52.9%		
					Likelihood ratio (a)		1.459		
					Asthma	Ref std +	Ref std –	Total	
					Br. rev. (b) +	87	33	120	
					Br. rev. (b) -	12	18	30	
					Total	99	51	150	
					Sensitivity (b)		87.9%		
					Specificity (b)		35.3%		
					Likelihood ratio (b)		1.359		
					Asthma	Ref std +	Ref std –	Total	
					Br. rev. (c) +	68	23	91	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
					Br. rev. (c) -	31	28	59	
					Total	99	51	150	
					Sensitivity (c) Specificity (c)		68.7% 54.9%		
					Likelihood ratio (c)		1.523		
					Asthma	Ref std +	Ref std –	Total	
					Br. rev. (d) +	73	22	95	
					Br. rev. (d) -	26	29	55	
					Total	99	51	150	
					Sensitivity (d) Specificity (d)		73.7% 56.9%		
					Likelihood ratio (d)		1.710		
					Asthma	Ref std +	Ref std –	Total	
					Br. rev. (e) +	80	28	108	
					Br. rev. (e) -	19	23	42	
					Total	99	51	150	
					Sensitivity(e) Specificity (e)		80.8% 45.1%		
					Likelihood ratio (e)		1.472		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
					Asthma	Ref std +	Ref std –	Total	
					Br. rev. (f) +	45	16	61	
					Br. rev. (f) -	54	35	89	
					Total	99	51	150	
					Sensitivity (f) Specificity (f)		45.5% 68.6%		
					Likelihood ratio (f)		1.449		

Table 48: CHHABRA 2005[310]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Chhabra SK. Acute bronchodilator response has limited value in differentiating bronchial asthma from COPD. J Asthma 2005; 42:	Study type:Diagnostic cross-sectional study Data source: Outpatient clinic Setting: Secondary care Country:	N = 354 Inclusion criteria: • Clinical diagnosis of asthma (non-smokers) or COPD; stable clinical state with no history of acute exacerbation in previous 4 weeks; acceptable performance of spirometry; FEV1/FVC ratio 70% or less	Male: Female Asthma: 122:78; COPD: 149:5 Mean age: Asthma mean 35.60 (12.47); COPD mean 56.28 (9.57) years Participants were already on (and remained on)	Index testBronchodilator reversibility: Response to inhaled salbutamol 200µg: a) absolute change in FEV1 (ΔFEV1); b) ΔFEV1%init; c) ΔFEV1%pred; d) ΔFEV1≥0.2l and ΔFEV1%init ≥12% **CUT-OFF:** positive = a) absolute change in FEV1 (ΔFEV1) a1: 0.2l; a2: 0.3l; a3: 0.4l; b) ΔFEV1%init b1: 12%; b2: 15%; b3: 20%; c) ΔFEV1%pred c1: 9%; c2: 15%; **d) ΔFEV1≥0.2l and ΔFEV1%init ≥12%** Reference standard**Clinical Dx**	**Asthma**	Ref std +	Ref std –	Total	Source of funding: Not stated Limitations: Time between index test and reference standard: unclear. Some exclusions may limit generalisability Additional data:
					Bronchodilator reversibility (a1) +	146	31	177	
					Bronchodilator reversibility (a1) -	54	123	177	
					Total	200	154	354	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
367-372. CHHABRA 2005	India <u>Recruitment:</u> Not stated.	<u>Exclusion criteria:</u> Smokers with asthma; any other concurrent pulmonary or systemic disease	corticosteroid treatment. BD Tx was withdrawn for 12 hrs.	Physician diagnosis based on clinical criteria suggested by the National Institute of Health Global Strategy for Asthma Management and Prevention (asthma = recurrent episodes of breathlessness and wheezing, with or without cough and phlegm, with seasonal and diurnal variations and any identifiable trigger factors) and the Global Initiative for Chronic Obstructive Lung Disease (COPD = history of smoking >10 pack-years, cough with expectoration for at least 3 consecutive months in a year for 2 years or more and progressive dyspnoea on exertion). Time between index test and reference standard: unclear <u>Target condition</u> Asthma	Sensitivity (a1) Specificity (a1)		73% 80%		Raw data not stated; calculated from sensitivity and specificity
					PPV (a1) NPV (a1) Likelihood ratio (a1)		82% 69% 3.60		
					Asthma	Ref std +	Ref std –	Total	
					Br. rev. (a2) +	106	20	126	
					Br. rev. (a2) -	94	134	228	
					Total	200	154	354	
					Sensitivity(a2) Specificity (a2)		53% 87%		
					PPV (a2) NPV (a2) Likelihood ratio (a2)		84% 59% 4.08		
					Asthma	Ref std +	Ref std –	Total	
					Br. rev. (a3) +	68	8	76	
					Br. rev. (a3) -	132	146	278	
					Total	200	154	354	
					Sensitivity (a3) Specificity (a3)		34% 95%		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
					PPV (a3) NPV (a3) Likelihood ratio (a3)		91% 53% 7.37		
					Asthma	Ref std +	Ref std –	Total	
					Br. rev. (b1) +	150	62	212	
					Br. rev. (b1) -	50	92	142	
					Total	200	154	354	
					Sensitivity (b1) Specificity (b1)		75% 60%		
					PPV (b1) NPV (b1) Likelihood ratio (b1)		71% 65% 1.88		
					Asthma	Ref std +	Ref std –	Total	
					Br. rev. (b2) +	132	48	170	
					Br. rev. (b2) -	68	106	174	
					Total	200	154	354	
					Sensitivity (b2) Specificity (b2)		66% 69%		
					PPV (b2) NPV (b2) Likelihood ratio		73% 61% 2.12		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
					(b2)				
					Asthma	Ref std +	Ref std –	Total	
					Br. rev. (b3) +	106	34	140	
					Br. rev. (b3) -	94	120	214	
					Total	200	154	354	
					Sensitivity (b3) Specificity (b3)		53% 78%		
					PPV (b3) NPV (b3) Likelihood ratio (b3)		76% 56% 2.42		
					Asthma	Ref std +	Ref std –	Total	
					Br. rev. (c1) +	126	25	151	
					Br. rev. (c1) -	74	129	203	
					Total	200	154	354	
					Sensitivity (c1) Specificity (c1)		63% 84%		
					PPV (c1) NPV (c1) Likelihood ratio (c1)		84% 64% 4.03		
					Asthma	Ref std +	Ref std –	Total	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
					Br. rev. (c2) +	76	8	84	
					Br. rev. (c2) -	124	146	270	
					Total	200	154	354	
					Sensitivity (c2) Specificity (c2)		38% 95%		
					PPV (c2) NPV (c2) Likelihood ratio (c2)		92% 54% 8.36		
					Asthma	Ref std +	Ref std –	Total	
					Br. rev. (d) +	130	29	159	
					Br. rev. (d) -	70	125	195	
					Total	200	154	354	
					Sensitivity (d) Specificity (d)		65% 81%		
					PPV (d) NPV (d) Likelihood ratio (d)		81% 64% 3.34		

Table 49: KIM 2012[861]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Kim T-B et al. The reality of an intermediate type between asthma and COPD in practice. Respir Care 2012; 57: 1248-1253. KIM2012	Study type:Diagnostic cross-sectional study Data source: Disease cohorts Setting: Secondary care Country: Republic of Korea Recruitment: Not stated	N = 514 Inclusion criteria: • Adults with chronic obstructive airways disorders included in an asthma cohort or a COPD cohort; all had at least one chronic persistent respiratory symptom (dyspnoea, cough, sputum production or wheeze) for >3 months or repetition of the symptom for >3 months Exclusion criteria: Patients with tuberculous destroyed lungs, bronchiectasis or lung resection	Male: Female 49% male in asthma group and 91.7% in COPD group Mean age: 48 (16) years for asthma and 65 (8) years for COPD	Index testBronchodilator reversibility: Bronchodilator response to albuterol 400µg **CUT-OFF:** positive = **Increase in FEV1 >200mL and >12% above baseline** Reference standard**Clinical Dx** Clinical decision (no definite diagnostic criteria) by specialists in allergy or pulmonary departments Time between index test and reference standard: same time Target condition Asthma	**Asthma**	Ref std +	Ref std –	Total	Source of funding: Korea Healthcare Technology Research and Development Project, Ministry of Health and Welfare, Republic of Korea Limitations: No definite diagnostic criteria used; unclear if index test could be part of diagnostic criteria. Some exclusions may limit generalisability Additional data: None
					Bronchodilator reversibility +	62	56	118	
					Bronchodilator reversibility -	307	89	396	
					Total	369	145	514	
					Sensitivity Specificity		16.8% 61.4%		
					PPV NPV		52% 22%		

Table 50: QUADRELLI 1999[1402]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Quadrelli SA et al. Evaluation of bronchodilator response in patients with airway obstruction. Respir Med 1999; 93: 630-636. QUADRELLI1999	Study type: Diagnostic cross-sectional study Data source: University hospital Setting: Secondary care Country: Argentina Recruitment: Not stated	N = 119 (subset of 61 patients with asthma with FEV1<55% from overall sample 142 asthma patients, plus all 58 patients with COPD) Inclusion criteria: • Patients with previously diagnosed airways obstruction; present baseline spirometry: FEV1/FVC relationship 1.64 SEE below predicted value or lower; people with asthma had FEV1 <55% predicted (to match with COPD patients' baseline lung function) Exclusion criteria:	Male: Female Overall: asthma 74:68; COPD 46:12 Mean age: Overall asthma: 55.4 (19.0) years; COPD 67.3 (7.0) years	• Index testBronchodilator reversibility: Response to inhaled salbutamol 200µg a) ΔFEV1[L]; b) ΔFEV1%init; c) ΔFEV1[L] plus ΔFEV1%init; d) ΔFEV1%pred; e) ΔFEV1%max (% of maximal possible response) **CUT-OFF:** positive = a) ΔFEV1[L]: 200mL; b) ΔFEV1%init: 15%; **c) ΔFEV1[L] >200mL plus ΔFEV1%init >15%;** d) ΔFEV1%pred: 9%; e) ΔFEV1%max (% of maximal possible response): 50% Positive and negative predictive values calculated for two arbitrary prevalences of asthma A] prevalence of asthma 30% and B] prevalence of asthma 70% Reference standard**Clinical Dx** Clinical diagnosis: asthma = attacks of breathlessness or wheeze according to ATS criteria (smokers excluded) and at least 2 of: 1;	**Asthma**	Ref std +	Ref std –	Total	Source of funding: Not stated Limitations: Time between index test and reference standard: unclear. Some exclusions may limit generalisability Additional data: Raw data not stated; calculated from sensitivity and specificity
					Br. rev. (a) +	43	17	60	
					Br. rev. (a) -	18	41	59	
					Total	61	58	119	
					Sensitivity (a)		70.4%		
					Specificity(a)		70.6%		
					PPV(a) [A] [B]		50.5% 84.8%		
					NPV (a) [A] [B]		84.7% 50.6%		
					Asthma	Ref std +	Ref std –	Total	
					Br. rev. (b) +	52	29	81	
					Br. rev. (b) -	9	29	38	
					Total	61	58	119	
					Sensitivity (b)		85.2%		
					Specificity(b)		50.0%		
					PPV(b) [A]		39.4%		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
		Those mentioned in inclusion and reference standard sections, plus patients not clearly classified as either asthma or COPD, or those under current treatment with systemic steroids		history of symptoms since childhood or adolescence; 2. symptomatic-free periods of >3 months; 3. spontaneous variations in FEV1 during the year of >20% of baseline value; 4. histamine challenge test <8mg/mL. COPD = heavy current or ex-smokers with no history of asthma reporting chronic cough or sputum (non-smokers excluded) Time between index test and reference standard: unclear <u>Target condition</u> Asthma	[B] NPV (b) [A] [B]		78.0% 82.9% 47.3%		
					Asthma	Ref std +	Ref std –	Total	
					Br. rev. (c) +	42	17	59	
					Br. rev. (c) -	19	41	60	
					Total	61	58	119	
					Sensitivity (c) Specificity(c)		68.8% 70.6%		
					PPV(c) [A] [B] NPV(c) [A] [B]		48.1% 83.5% 81.9% 45.5%		
					Asthma	Ref std +	Ref std –	Total	
					Br. rev. (d) +	41	17	58	
					Br. rev. (d) -	20	41	61	
					Total	61	58	119	
					Sensitivity (d) Specificity(d)		67.2% 70.6%		
					PPV(d) [A] [B] NPV (d) [A]		49.2% 84.1% 83.1%		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
					[B]		47.5%		
					Asthma	Ref std +	Ref std –	Total	
					Br. rev. (e) +	4	1	5	
					Br. rev. (e) -	57	57	114	
					Total	61	58	119	
					Sensitivity (e) Specificity(e)		6.5% 98.2%		
					PPV(e) [A] [B] NPV (e) [A] [B]		75.5% 94.5% 72.3% 32.4%		

G.7 PEF variability

Table 51: BROUWER 2010[233]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Brouwer AFJ, Visser CAN, Duiverman EJ,	Study type:DiagnosticCross-sectional study	N = 61 Inclusion criteria: Children with non-specific respiratory	Male: Female 27:34 Mean age: 6 to 16 years;	Index testPEF variation amp%mean **CUT-OFF:** positive = >95th centile for healthy children i.e. ≥12.3%	**Asthma**	Ref std +	Ref std –	Total	Source of funding: AstraZeneca NL Limitations:
					PEF +	10	11	21	
					PEF -	10	28	38	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Roorda RJ, and Brand PLP. Is home spirometry useful in diagnosing asthma in children with nonspecific respiratory symptoms? Pediatric Pulmonology2010; 45: 326-332 REF ID: **BROUWER2010**.	Data source: Paediatric asthma clinic Setting: Secondary care Country: The Netherlands Recruitment: Not stated.	symptoms such as cough and breathlessness in whom GP uncertain of diagnosis referred to hospital-based paediatric asthma clinic Exclusion criteria: Straightforward diagnosis of asthma based on classical respiratory symptoms; referred for poorly controlled asthma; systemic corticosteroids or long-acting beta-2 agonists in last 4 weeks	mean 10.4 years	Reference standard**Clinical Dx**including objective test: Asthma diagnosed by paediatric pulmonologist including history. physical examination and lung function tests including methacholine challenge Time between index test and reference standard: same time Target condition Asthma	Total	20	39	59	Home spirometry data lost for 2 patients due to battery failure of the device Additional data: None
					Sensitivity		50%		
					Specificity		72%		
					PPV		48%		
					NPV		74%		
					Likelihood ratio		1.77		

Table 52: DEN OTTER 1997[417]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
den Otter JJ, Reijnen GM, van den Bosch	Study type:DiagnosticCross-sectional	N = 323 Inclusion criteria: adults between 25	Male: Female 135:188 Mean age:	Index testPEF variability = ($PEF_{highest}$ – PEF_{lowest})/ PEF_{mean} x 100% (mean over 21 days' readings)	**Asthma**	Ref std +	Ref std –	Total	Source of funding: Not stated.
					PEF var >15%	6	4	10	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
WJ, van Schayck CP, Molema J, Van Weel C. Testing bronchial hyper-responsiveness: provocation or peak expiratory flow variability ? British Journal of General Practice. 1997; 47(421):487-492 DENOTTE R1997	study Data source: Population screening Setting: General population Country: The Netherlands Recruitment: Not stated.	and 70 years old with signs or symptoms indicating asthma (persistent or recurrent respiratory symptoms or signs of reversible bronchial obstruction) Exclusion criteria: None given	43 (12) years	**CUT-OFF:** positive = >5% or 10% or 15% Reference standard**Clinical Dx**including objective test: Reference standard = BHR, defined as a PC20 histamine of ≤8 mg/ml Time between index test and reference standard: unclear Target condition Asthma	PEF var ≤15%	124	184	308	Limitations: None Additional data:None
					Total	130	188	318	
					Sensitivity Specificity		5% 97%		
					PPV NPV PLR and NLR		60% 60%		
						Ref std +	Ref std –	Total	
					PEF var >10%	18	8	26	
					PEF var ≤10%	112	180	292	
					Total	130	188	318	
					Sensitivity Specificity		14% 96%		
					PPV NPV PLR and NL		69% 62%		
						Ref std +	Ref std –	Total	
					PEF var >5%	73	58	131	
					PEF var ≤5%	57	130	187	
					Total	130	188	318	
					Sensitivity		56%		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
					Specificity	69%	
					PPV NPV PLR and NL	56% 66%	

Table 53: THIADENS 1998[1727]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Thiadens HA, De Bock GH, Dekker FW, Huysman JA, Van Houwelingen JC, Springer MP et al. Value of measuring diurnal peak flow variability in the recognition of asthma: a study in general practice.	Study type:Diagnostic Cross-sectional study Data source: Community Setting: Primary care Country: The Netherlands Recruitment: January 1994 – March 1995	N = 170 Inclusion criteria:18–75 yrs of age, who consulted their GP with coughing that had lasted for at least 2 weeks Exclusion criteria: Already had a diagnosis of asthma or COPD, pregnant, or had a cardiovascular or concomitant pulmonary disease	Male: Female 61: 109 Mean age: 44 (16) years	Index test: PEF variability (DPV) = ($PEF_{highest}$ – PEF_{lowest})/ $PEF_{highest}$ x 100% = amplitude % highest (a) MDPV = mean over 2 week period (b) DPV more than threshold on 4 days or more (c) DPV more than threshold on 3 days or more **CUT-OFF:** (a) MDPV > 10% and MDPV >15% (b) DPV >15% on 4 days or more (c) DPV >20% on 3 days or more Reference standard**Clinical Dx**including objective test: A patient was considered to have asthma if there had been a		Ref std +	Ref std –	Total	Source of funding: GlaxoWellcome BV, Medical Division, The Netherlands. Limitations: Sensitivity etc calculated Additional data: None
					MDPV (a) >10% +	10	3	13	
					MDPV -	59	98	157	
					Total	69	101	170	
					Sensitivity Specificity		14.5% 97.0%		
					PPV NPV PLR and NL		76.9% 62.4%		
						Ref std +	Ref std –	Total	
					MDPV (a) 15% +	2	1	3	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
European Respiratory Journal. 1998; 12(4):842-847 THIADENS 1998				previous period of respiratory symptoms for >3 weeks in the last year, accompanied by a provocative dose causing a 20% fall in FEV1 (PD20) ≤15.6 µmol methacholine and/or reversibility ≥9% of predicted Time between index test and reference standard: same time <u>Target condition</u> Asthma	MDPV -	67	100	167	
					Total	69	101	170	
					Sensitivity Specificity		2.9% 99.0%		
					PPV NPV PLR and NL		66.7% 59.9%		
						Ref std +	Ref std –	Total	
					DPV(b) >15% ≥4 days +	14	3	17	
					PEF -	55	98	153	
					Total	69	101	170	
					Sensitivity Specificity		20.3% 97.0%		
					PPV NPV PLR and NL		82.4% 64.1%		
						Ref std +	Ref std –	Total	
					DPV (c)	8	1	9	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
					>20% on ≥3 days +				
					PEF -	61	100	161	
					Total	69	101	170	
					Sensitivity Specificity		11.6% 99.0%		
					PPV NPV PLR and NL		88.9% 62.1%		

Table 54: ULRIK 2005[1789]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Ulrik CS, Postma DS, Backer V. Recognition of asthma in adolescents and young adults: which objective measure is best? Journal of	Study type: Diagnostic Cross-sectional study Data source: Community survey Setting: Community Country:	N = 74 people with asthma out of sample of 609 adolescents and young adults in survey Inclusion criteria: Children and adolescents born between 1969 and 1979 in central Copenhagen Exclusion criteria: None given	Male: Female 37:37 Mean age: 18.5 (2.8) years	Index testPEF variability (amp%mean) **CUT-OFF:** positive = PEF amp%mean ≥20% Reference standard**Clinical Dx**including objective test: 1) Histamine challenge test; cut off PC20 <16.0mg/mL histamine (airways hyper-responsiveness) 2) Bronchodilator reversibility: change in FEV1 (ΔFEV1%post) >10%	**Asthma**	Ref std (1) +	Ref std (1) –	Total	Source of funding: Danish Lung Association Limitations: Asthma patients only Additional data: None
					PEF +	32	1	33	
					PEF -	37	4	41	
					Total	69	5	74	
					Sensitivity Specificity		46.4% 80.0%		
					PPV NPV PLR and NLR		97.0% 9.8%		
					AUC				

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Asthma. 2005; 42(7):549-554 ULRIK2005	Denmark <u>Recruitment:</u> 1992.			Time between index test and reference standard: same time <u>Target condition</u> Asthma	Diagnostic yield				
						Ref std (2) +	Ref std (2) –	Total	
					PEF +	5	28	33	
					PEF -	2	39	41	
					Total	7	67	74	
					Sensitivity Specificity		71.4% 58.2%		
					PPV NPV PLR and NL		15.2% 95.1%		
					AUC				
					Diagnostic yield				

G.8 Skin prick tests

Table 55: DRKULEC 2013[451]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Sensitization profile in differential diagnosis: allergic	<u>Study type:</u> Diagnostic Cross-sectional study <u>Data source:</u>	N = 131 (N=71 asthma) <u>Inclusion criteria:</u> • 1-15 year olds in Zagreb	<u>Male: Female</u> 89:32 <u>Mean age:</u> 7.5 years	<u>Index test</u> **SPT** • Allergopharma (Croatia) • Allergens: • SPT for *Dermatophagoides pteronyssinus* (house dust	**Der P**	Asthma	Chronic cough	Total	<u>Source of funding:</u> Departmental sources
					SPT +	59	17	76	
					SPT -	12	43	55	
					Total	71	60	131	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
asthma vs. chronic (nonspecific) cough syndrome. Medical science monitor: 19: 409-415 Drkulec V, Nogalo B, Perica M, Plavec D, Pezer M, and Turkalj M 2013. REF ID: DRKULEC2013.	Clinic Setting: Patients attending Department of Allergology Country: Croatia Recruitment: 6 month period (date not stated)	• Respiratory symptoms • Sent to department for diagnosis Exclusion criteria: None given		mite) • *Ambrosia artemisifoliae* (common ragweed) • *Phleum pratense* (timothy grass) **CUT-OFF:** not stated. Reference standard **Clinical Dx** At least 3 episodes of wheezing and/or positive bronchodilatation test Time between index test and reference standard: same time Target condition Allergic asthma (vs. chronic cough, i.e. <3 episodes of wheezing, with persistent cough >6 weeks)	**Der P** Sensitivity Specificity		 83.6% (72.4, 90.8) 71.4% (59.9, 80.7)		Limitations: none Additional data: Raw data calculated not presented
					PPV NPV Likelihood + test Likelihood - test		71.8% (60.5, 80.9) 83.3% (71.9, 90.7) 2.9 (2.6, 3.3) 0.23 (0.19, 0.28)		
					Diagnostic accuracy		77.1% (69.2, 83.5)		
					Diagnostic odds		12.8 (5.4, 29.9)		
					Amb A	Asthma	Chronic cough	Total	
					SPT +	47	31	78	
					SPT -	24	29	53	
					Total	71	60	131	
					Amb A Sensitivity Specificity		 66.7% (46.7, 82.0) 48.6% (39.3, 57.9)		
					PPV NPV Likelihood + test Likelihood - test		22.5% (14.4, 33.5) 86.7% (75.8, 93.1) 1.30 (1.18, 1.4) 0.69 (0.52, 0.91)		
					Diagnostic accuracy		51.9% (43.4, 60.3)		
					Diagnostic odds		1.89 (0.75, 4.8)		
					Phl P	Asthma	Chronic cough	Total	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
					SPT +	47	30	77	
					SPT -	24	30	54	
					Total	71	60	131	
					Phl P Sensitivity Specificity		66.7% (48.8, 80.8) 49.5% (39.9, 59.1)		
					PPV NPV Likelihood + test Likelihood - test		28.2% (19.0, 39.5) 83.3% (71.9, 90.7) 1.3 (1.2, 1.4) 0.67 (0.53, 0.85)		
					Diagnostic accuracy		53.4% (44.9, 61.8)		
					Diagnostic odds		1.96 (0.84, 4.60)		
					≥1 allergens	Asthma	Chronic cough	Total	
					SPT +	56	5	61	
					SPT -	15	55	70	
					Total	71	60	131	
					SPT to ≥1 allergen Sensitivity Specificity		78.8% (68.9, 86.2) 91.3% (79.7, 96.6)		
					PPV NPV Likelihood + test Likelihood - test		94.4% (86.4, 97.8) 70% (57.5, 80.1) 9.1 (5.5, 14.9) 0.23 (0.21, 0.26)		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
					Diagnostic accuracy	83.21% (75.88, 88.64)	
					Diagnostic odds	39.1 (12.4, 123.4)	

Table 56: Gaig 1999[533]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Asthma, mite sensitization, and sleeping in bunks. Annals of allergy, asthma and immunology: 82: 531-533 Gaig P, Enrique E, Garcia-Ortega P, Olona M, del Mar San Miguel M, and Richart C 1999.	Study type: Cross-sectional study Data source: Clinic Setting: Outpatient allergy clinic Country: Spain Recruitment: Consecutive patients, date not stated	N = 94 (47 sibling pairs); (N=41 asthma) Inclusion criteria: Patients attending outpatient allergy clinic who had been sharing a bunk with a sibling for >6 months, occupying always the same position (top or bottom bunk) Exclusion criteria: not stated	Male: Female 43:51 Mean age: 16 years	Index test **SPT** • ALK Abelló (Madrid, Spain) • Allergens: • *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* **CUT-OFF:** skin wheal diameter to at least one of the two mites 3mm larger than control Reference standard **Clinical Dx** Clinical history and current symptoms (asthma or rhinitis) Time between index test and reference standard: not stated Target condition Allergic asthma (vs. rhinits)	**Der P/ Der F**	Asthma	Rhinitis	Total	Source of funding: ALK Abelló (Madrid, Spain) supported antibody testing Limitations: No mention of objective test for asthma; study not designed to assess diagnostic test Additional data: Sensitivity etc calculated from 2 x 2 table
					SPT +	35	17	52	
					SPT -	6	9	15	
					Total	41	26	67	
					Mite Sensitivity		85.4%		
					Specificity		34.6%		
					PPV		67.3%		
					NPV		60%		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
REF ID: GAIG1999.							

Table 57: May 1990[1096]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Allergy to Artemisia vulgaris in the region of Warsaw. Allergologia et Immunopathologia: 18: 57-60 May KL 1990. REF ID: MAY1990.	Study type: Diagnostic Cross-sectional study Data source: Clinic Setting: Allergology clinic Country: Poland Recruitment: consecutive patients, date not stated	N = 446 (N=190 asthma) Inclusion criteria: Consecutive unselected patients for allergological consultation for conjunctivitis, rhinitis and/or asthma which appeared or deteriorated in late spring and summer Exclusion criteria: None stated	Male: Female 256:190 Mean age: Range 6 to 56 years, mean not stated	Index test **SPT** • Haarlem-Holland • Allergens: • *Gramineae* (grasses both wild and cultivated) • *Artemisia vulgaris* (weed: mugwort) **CUT-OFF:** 3+ or 4+ Reference standard **Clinical Dx** Clinically evident bronchial symptoms Time between index test and reference standard: not stated Target condition Asthma with or without	**Gramineae**	Asthma with or without rhinitis and with or without conjunctivitis	Rhinitis with or without conjunctivitis	Total	Source of funding: Not stated Limitations: No mention of objective test for asthma
					SPT +	170	228	398	
					SPT -	20	28	48	
					Total	190	256	446	
					Gramineae Sensitivity Specificity		89.5% 10.9%		Additional data: Sensitivity etc calculated from 2 x 2 table
					PPV NPV		42.7% 58.3%		
					Artemisia vulgaris	Asthma	Rhinitis	Total	
					SPT +	92	95	187	
					SPT -	98	161	259	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
				rhinitis and with or without conjunctivitis (vs. rhinitis with or without conjunctivitis.)	Total	190	256	446	
					Artemisia vulgaris Sensitivity Specificity		48.4% 62.9%		
					PPV NPV		49.2% 62.2%		

Table 58: Miraglia del Giudice 2002[1144]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Atopy and house dust mite sensitization as risk factors for asthma in children. Allergy: 57: 169-172 Miraglia Del Giudice M, Pedulla M, Piacentini GL,	Study type: Diagnostic Cross-sectional study Data source: Clinic Setting: Paediatric Asthma and Allergy clinic Country: Italy	N = 1426 (N=925 asthma) Inclusion criteria: Children referred to our Paediatric Asthma and Allergy Centre because of allergic symptoms (see reference standard) Exclusion criteria: Children without a confirmed	Male: Female 814:612 Mean age: Range 0 to 12 years, mean not stated	Index test **SPT** • Bayer DHS Diagnostics, Epernon Cedex-France • Allergens: • house dust mites (HDM) (*Dermatophagoides pteronyssinus, D. farinae*), *Parietaria officinalis* (lichwort, in the nettle family), grasses (*Dactylis glomerata, Lolium perenne, Phaleum pratense*), moulds (*Alternaria, Aspergillus, Cladosporium*), dog fur, cat fur, egg albumin, and cow's milk **CUT-OFF:** wheal was at least 3 mm in diameter Reference standard **Clinical Dx** Clinical diagnosis: asthma, allergic	**≥1 test +ve**	Asthma	Chronic cough	Total	Source of funding: None stated
					SPT +	411	218	629	
					SPT -	514	283	797	
					Total	925	501	1426	
					≥1 test +ve Sensitivity Specificity		44% 56%		Limitations: No mention of objective test for asthma Additional data: Sensitivity,
					PPV NPV		65% 36%		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Capristo C, Brunese FP, Decimo F, Maiello N, and Capristo AF 2002. REF ID: MIRAGLIA DELGIUDICE2002.	Recruitment: January–December 1998	diagnosis		rhinoconjunctivitis, atopic dermatitis and food allergy was confirmed by a paediatric allergologist. **Bronchial asthma** defined as ≥3 episodes of wheezing < 2 years of age, or 1 episode from 2 years of age, or any episode of wheezing independent of age, if combined with atopic symptoms in the family or other atopic symptoms in the child. **Allergic rhino-conjunctivitis:** sneezing, nasal obstruction, watery rhinorrhea, nasal itching, conjunctival hyperemia and photophobia at least twice after exposure to a particular allergen and unrelated to infection. **Food allergy:** acute onset of symptoms e.g. skin reactions, wheezing, oral allergic symptoms, vomiting or diarrhoea on >1 occasion after ingestion of, or oral contact with, a particular type of food. **Atopic dermatitis:** defined according to Hanifin and assessed with the Scorad index Time between index test and reference standard: not stated Target condition Allergic asthma (vs. allergic rhinoconjunctivitis, atopic dermatitis or			specificity calculated

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
				food allergy)			

Table 59: Popovic 2002[1367]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
S. Popovic-Grle, M. Mehulic, F. Pavicic, I. Babic, and Z. Beg-Zec. Clinical validation of bronchial hyperresponsiveness, allergy tests and lung function in the diagnosis of asthma in persons with dyspnea. *Coll.Antro*	Study type: Cross-sectional study Data source: Random sample Setting: Outpatient allergy department Country: Croatia Recruitment: Just says 'sample' of patients, date not stated	N = 195 (N=141 asthma, n=17 COPD, n=29 rhinitis/sinusitis, n=8 unsolved) Inclusion criteria: • Pts with dyspnoea • Treated for breathlessness in the Outpt dept of Allergology • Referred by GPs due to suspected asthma Exclusion criteria: • All serious diseases of other organ systems or the lungs (apart from those of an obstructive and/or	**ASTHMA PTS:** Male: Female 51%:49% Mean age: 36.5 years	Index test **SPT** • House dust • *D. pteronyssinus* • Grass pollen • Weed pollen • Tree pollen • Animal dander • Cat fur • Dog fur • Feathers • Fungi mixture • Insect antigens **CUT-OFF:** skin wheal diameter ≥3mm. Reference standard **Clinical Dx (with obj test)** Questionnaire of clinical history of occasional asthma attacks with wheezing and nocturnal awakening because of dyspnoea, and BDR test with salbutamol.	**≥1 aeroallergen**	Asthma	Non-asthma	Total	Source of funding: None reported Limitations: No major ones identified
					SPT +	87	20	1074	
					SPT -	54	34	88	
					Total	141	54	195	
					Sensitivity Specificity		62% 63%		
					PPV NPV		81% 61%		
									Additional data: n/a

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
pol. 26 Suppl:119 -127, 2002. REF ID: POPOVIC 2002.		allergic nature)		Time between index test and reference standard: not stated Target condition Allergic asthma (vs. rhinitis/sinusitis, COPD or unsolved)			

Table 60: Soriano 1999A[1628]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
JB Soriano, JM. Anto, J. Sunyer, A. Tobias, M. Kogevinas, E. Almar, N. Muniozguren, JL. Sanchez, L. Palenciano, P. Burney, J. Martinez-Moratalla et al. Risk of asthma in the general Spanish	Study type: Cross-sectional study Data source: Sub sample of general population reporting respiratory symptoms Setting: General population	N = 1816 (N=136 asthma) Inclusion criteria: • Subsample of pts from a general population, who reported respiratory symptoms in a screening questionnaire. Exclusion criteria: • Already selected in	Male: Female 48%:52% Mean age: 32 years	Index test **SPT** • *D. pteronyssinus* • *Cladosporium* • *Alternaria* • Timothy grass • Olive • Birch • Parieta or ragweed **CUT-OFF:** skin wheal diameter ≥3mm. Reference standard **Clinical Dx with objective test** Clinical history and current symptoms (woken up by attack of	**≥1 allergen +ve**	Asthma	Non-asthma	Total	Source of funding: Fondo de Investigaciones Sanitarias, Madrid and Generalitat de Catalunya.
					SPT +	60.7% (n=83)	31.4% (n=528)	611	
					SPT -	39.3% (n=53)	68.6% (n=1152)	1205	
					Total	136	1680	1816	
					Sensitivity Specificity		60.7% 68.6%		
					PPV NPV		- -		
					Alternaria	Asthma	Non-asthma	Total	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
population attributable to specific immunoresponse. *Int.J.Epidemiol.* 28 (4):728-734, 1999. REF ID: SORIANO 1999A.	<u>Country:</u> Spain <u>Recruitment:</u> date not stated	an earlier random sample		shortness of breath during last 12 months, or having an attack of asthma during last 12 months, or currently taking medication for asthma) – using questionnaire, plus methacholine challenge for bronchoresponsiveness (BR). Asthma defined as symptomatic BR. Time between index test and reference standard: not stated <u>Target condition</u> Allergic asthma	SPT +	6.7% (n=9)	1.4% (n=24)	33	
					SPT -	93.3% (n=127)	98.6% (n=1656)	1783	
					Total	136	1680	1816	
					Sensitivity Specificity		6.7% 98.6%		
					Birch	Asthma	Non-asthma	Total	
					SPT +	5.9% (n=8)	1.6% (n=27)	35	
					SPT -	94.1% (n=128)	98.4% (n=1653)	1781	
					Total	136	1680	1816	
					Sensitivity Specificity		5.9% 98.4%		
					Cat	Asthma	Non-asthma	Total	
					SPT +	20.7% (n=28)	6.3% (n=106)	134	
					SPT -	79.3% (n=108)	93.7% (n=1574)	1682	
					Total	136	1680	1816	
					Sensitivity Specificity		20.7% 93.7%		
					Cladosporium	Asthma	Non-asthma	Total	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
					SPT +	7.4% (n=10)	2.8% (n=47)	57	
					SPT -	92.6% (n=126)	97.2% (n=1633)	1759	
					Total	136	1680	1816	
					Sensitivity Specificity		7.4% 97.2%		
					Dust mite	Asthma	Non-asthma	Total	
					SPT +	39.3% (n=53)	20.0% (n=336)	389	
					SPT -	60.7% (n=83)	80.0% (n=1344)	1427	
					Total	136	1680	1816	
					Sensitivity Specificity		39.3% 80.0%		
					Timothy grass	Asthma	Non-asthma	Total	
					SPT +	31.9% (n=43)	13.3% (n=223)	266	
					SPT -	68.1% (n=93)	86.7% (n=1457)	1550	
					Total	136	1680	1816	
					Sensitivity Specificity		31.9% 86.7%		

G.9 IgE

Table 61: ABRAHAM 2007[8]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
CM. Abraham, DR Ownby, EL Peterson, G Wegienka, EM Zoratti, LK Williams, CLM Joseph, and C Cole Johnson. The relationship between seroatopy and symptoms of either allergic rhinitis or asthma. *J.Allergy Clin.Immunol.* 119 (5):1099-1104, 2007.	Study type:Diagnostic Cross-sectional study Data source: Information from a regional survey of pregnant women in a primary care practice, and subsequent interview and blood test. Setting: Primary care Country:USA Recruitment: Dates not	N = 702 Inclusion criteria: • Pregnant women in second trimester or later • Age 21-49 years Exclusion criteria: None given	Male: Female 0 : 100% Mean age: 29 years Dx of asthma: N=140 self-reported, N=138 physician provided Dx.	Index test**Specific IgE** • Pharmacia UniCAP system • Allergens: ○ Dust mite (American) *D. farinae* ○ Dust mite (European) *D. pteronyssinus* ○ Cat ○ Dog ○ Cockroach ○ Ragweed ○ Grass (timothy) ○ Egg ○ *Alternaria* **CUT-OFF:** positive = ≥0.35 kU/l. Reference standard**Clinical Dx** Physician Dx of asthma (by answer to questionnaire). Time between index test	**Dust mite (Ameri) asthma**	Ref std +	Ref std –	Total	Source of funding: National Institute of Allergy and Infectious Diseases and by the Fund for Henry Ford Health System, Detroit. Limitations: High IgE cut off, pregnant women only, consecutive recruitment; Unclear time between Ref standard and Index test
					IgE +				
					IgE -				
					Total				
					Sensitivity Specificity				
					Dust mite (Euro) asthma	Ref std +	Ref std –	Total	
					IgE +	37.9% (~n=47)	21.8% (~n=90)		
					IgE -	62.1% (~n=77)	78.2% (~n=403)		
					Total	N=124	N=493	N=617	
					Sensitivity Specificity		37.9 (47/124) 78.2 (97/493)		
					Grass (tim)	Ref std +	Ref std –	Total	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
ABRAHAM 2007	given			and reference standard:Index done much later (because physican Dx was determined by people answering a questionnaire, so the Dx could have been made any previous time) Target condition Allergic asthma	**asthma**				Additional data:
					IgE +	33.3% (~n=41)	19.5% (~n=96)		
					IgE -	66.7% (~n=83)	80.5% (~n=397)		
					Total	N=124	N=493	N=617	
					Sensitivity Specificity		33.3 (41/124) 80.5 (397/493)		
					***Alternaria*asthma**	Ref std +	Ref std –	Total	
					IgE +	33.9% (~n=42)	14.4% (~n=71)		
					IgE -	66.1% (~n=82)	85.6% (~n=422)		
					Total	N=124	N=493	N=617	
					Sensitivity Specificity		33.9 (167/124) 85.6 (106/493)		
					Cat asthma	Ref std +	Ref std –	Total	
					IgE +	39.8% (~n=49)	12.2% (~n=60)		
					IgE -	(~n=75)	87.8% (~n=433)		
					Total	N=124	N=493	N=617	
					Sensitivity Specificity		39.8% 87.87%		
					Dog asthma	Ref std +	Ref std –	Total	
					IgE +	33.9%	12.3%		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
						(~n=42)	(~n=61)		
					IgE -	66.1% (~n=82)	88% (~n=432)		
					Total	N=124	N=493		
					Sensitivity Specificity		33.9% 88%		

Table 62: LINNEBERG 2006[1015]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
A. Linneberg, L. Husemoen, N. Nielsen, F. Madsen, L. Frolund, and N. Johansen. Screening for allergic respiratory disease in the general population with the ADVIA Centaur Allergy Screen Assay. *Allergy* 61 (3):344-348, 2006.	Study type:Diagnostic Cross-sectional study Data source: Random sample from a prospective cohort study (Copenhagen Allergy Study). Setting: General population Country:Denmark	N = 709 Inclusion criteria: • 15-69 year olds in Copenhagen • Participants in the study who responded at follow-up • Random group and a respiratory symptom group were used for analysis	Male: Female Not reported Mean age: Not reported	Index test**Specific IgE** • ADIVA Centaur immunoassay • Allergens: ○ Birch ○ Grass (timothy) ○ Mugwort ○ Mammals (includes dog, cat, horse, hamster and others) ○ Dust mite **CUT-OFF:** positive = >0.35 kU/l. Reference standard**Clinical Dx** Allergic asthma clinical Dx by presence of positive symptoms (via questionnaire) and positive SPT. Time between index test and	**Pollen asthma**	Ref std +	Ref std –	Total	Source of funding: Not stated Limitations: Unclear time between Ref standard and Index test
					IgE +	49	238	287	
					IgE -	2	420	422	
					Total	51	658	709	
					Sensitivity Specificity		96.1 (49/51) 63.8 (420/658)		
					PPV NPV PLR and NLR		17.1 (49/287) 99.5 (420/658) -		
					Dust mite asthma	Ref std +	Ref std –	Total	
					IgE +	27	260	287	
					IgE -	5	417	422	
					Total	32	677	709	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
LINNEBERG 2006	Recruitment: Oct 1997-Nov 1998	Exclusion criteria: None given		reference standard: unclear Target condition Allergic asthma	Sensitivity Specificity		84.4 (27/32) 62.0 (417/677)		Additional data:
					PPV NPV		9.4 (27/287) 61.5 (417/677)		
					ALL allergic asthma	Ref std +	Ref std –	Total	
					IgE +	79	208	287	
					IgE -	6	416	422	
					Total	85	624	709	
					Sensitivity Specificity		92.9 (79/85) 66.7 (416/624)		
					PPV NPV PLR and NLR		27.5 (79/287) 98.6 (416/422) -		

Table 63: PLASCHKE 1999A[1354]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
P. Plaschke, C. Janson, E. Norrman, E. Björnsson, S. Ellbjär, and B. Järvholm. Association between atopic sensitization	Study type:DiagnosticCross-sectional study Data source: Random sample(1800 men, 1800 women) from population registers.	N = 1572 in final analysis. Inclusion criteria: • Aged 20-44 years • Responded to questionnaire and agreed to	Male: Female 46: 54% Mean age: 33 years Current smokers: 30%	Index test**Specific IgE** • Pharmacia CAP system • Allergens: ○ Cat ○ Dust mite *D. pteronyssinus* ○ Grass ○ Birch	**Dust mite (Euro) asthma**	Ref std +	Ref std –	Total	Source of funding: Fondo de Investigaciones Sanitarias, Madrid and Generalitat de Catalunya.
					IgE +	18.8% (~n=16)	5.8% (~n=86)	102	
					IgE -	81.2% (~n=68)	94.2% (~n=1402)	1470	
					Total	N=84	N=1488	N=1572	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
and asthma and bronchial hyperresponsiveness in swedish adults: pets, and not mites, are the most important allergens. *J.Allergy Clin.Immunol*. 104 (1):58-65, 1999. PLASCHKE 1999A	Postal questionnaire (modified ECRHS) was sent and had an 86% response rate. 89.2% of those who answered, agreed to participate in clinical examinations. Setting: General population Country: Sweden Recruitment: Feb 1991 – June 1992	have clinical examination and perform SPT, RAST and bronchial methacholine challenge. Exclusion criteria: None given	Dx of asthma: N=84 (according to symptoms and previous Dx ascertained by questionnaire).	○ *Cladosporium* **CUT-OFF:** positive = class ≥2 (≥0.7 kU/l). Reference standard**Clinical Dx** Dx of asthma (by answer to questionnaire) Time between index test and reference standard:Not mentioned. Target condition Allergic asthma	Sensitivity Specificity		18.8 (16/84) 94.2 (1402/1488)		
					Grass asthma	Ref std +	Ref std –	Total	Limitations: High IgE cut off; Unclear time between Ref standard and Index test
					IgE +	35.3% (~n=30)	12.6% (~n=187)	217	
					IgE -	64.7% (~n=54)	87.3% (~n=1301)	1355	
					Total	N=84	N=1488	N=1572	
					Sensitivity Specificity		35.3 (30/84) 87.3 (1301/1572)		Additional data:
					Birch asthma	Ref std +	Ref std –	Total	
					IgE +	29.4% (~n=25)	10.4% (~n=155)	180	
					IgE -	70.6% (~n=59)	89.6% (~n=1333)	1392	
					Total	N=84	N=1488	N=1572	
					Sensitivity Specificity		29.4 (25/84) 89.6 (1333/1488)		
					***Cladosporium* asthma**	Ref std +	Ref std –	Total	
					IgE +	3.5% (~n=3)	1.0% (~n=15)	18	
					IgE -	96.5% (~n=81)	99.0% (~n=1473)	1554	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
					Total	N=84	N=1488	N=1572	
					Sensitivity Specificity		3.5 (3/84) 99.0 (1473/1488)		
					Cat asthma	Ref std +	Ref std –	Total	
					IgE +	40% (~n=34)	9.4% (~n=140)		
					IgE -	60% (~n=50)	90.6% (~n=1348)		
					Total	N=84	N=1488		
					Sensitivity Specificity		40% 90.6%		

Table 64: SORIANO 1999[1627]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
J. B. Soriano, J. M. Anto, J. Sunyer, A. Tobias, et al. Risk of asthma in the general Spanish population attributable to	Study type:DiagnosticCross-sectional study Data source: Info from a 20% random subsample of a qu'aire	N = 1816 Inclusion criteria: • Aged 20-44 years • Responded to questionnaire and provided blood samples, had SPTs and spirometry as	Male: Female 48 : 52% Mean age: 32 years Current smokers: 52%	Index test**Specific IgE or SPT** • Pharmacia CAP system • Allergens: ○ Cat ○ *Cladosporium* ○ Dust mite *D. pteronyssinus* ○ Grass (timothy) ○ *Parietaria* ○ *Alternaria* (SPT only)	***Cladosporium* asthma**	Ref std +	Ref std –	Total	Source of funding: Fondo de Investigaciones Sanitarias, Madrid and Generalitat de Catalunya.
					IgE +	7.4% (~n=10)	2.8% (~n=47)	57	
					IgE -	92.6% (~n=126)	97.2% (~n=1633)	1759	
					Total	N=136	N=1680	N=1816	
					Sensitivity / Specificity		7.0 and 97.2		
					Dust mite asthma	Ref std +	Ref std –	Total	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
specific immunoresponse. Spanish Group of the European Community Respiratory Health Survey. *Int.J.Epidemiol.* 28 (4):728-734, 1999. SORIANO 1999	given toa random sample (N=16844) of general pop. aged 20-44 yrs in 5 areas of Spain. <u>Setting:</u> General population <u>Country:</u>Spain <u>Recruitment:</u> Dates not given	well as methacholine challenge test. <u>Exclusion criteria:</u> None given	<u>Dx of asthma:</u> N=136 (according to symptoms and BR results) performed by the study and questionnaire. N=1689 (not asthma).	○ Birch (SPT only) ○ Olive Ragweed (SPT only) **CUT-OFF:** positive = >0.35 kU/l. <u>Reference standard</u>**Clinical Dx** Dx of asthma (by answer to questionnaire and BR results). <u>Time between index test and reference standard:</u>Index done same time as BR tests <u>Target condition</u> Allergic asthma	IgE +	39.3% (~n=53)	20.0% (~n=336)	389	<u>Limitations:</u> Unclear time between Ref standard and Index test; results mix of IgE + SPT. <u>Additional data:</u>
					IgE -	60.7% (~n=83)	80.0% (~n=1344)	1427	
					Total	N=136	N=1680	N=1816	
					Sensitivity Specificity		39.3 (53/136) 80.0 (1344/1680)		
					Grass timothy asthma	Ref std +	Ref std –	Total	
					Index test +	31.9% (~n=93)	13.3% (~n=223)	316	
					Index test -	68.1% (~n=43)	86.7% (~n=1457)	1500	
					Total	N=136	N=1680	N=1816	
					Sensitivity Specificity		68.0 (93/136) 86.7 (1457/1680)		
					Cat asthma	Ref std +	Ref std –	Total	
					IgE +	20.7% (~n=27)	6.3% (~n=106)		
					IgE -	79.3% (~n=109)	93.7% (~n=1574)		
					Total	136	1680		
					Sensitivity Specificity		20.7% 94%		

Table 65: TSCHOPP 1998[1768]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
J. M. Tschopp, D. Sistek, C. Schindler, P. Leuenberger, A. P. Perruchoud, B. Wuthrich, M. Brutsche, J. P. Zellweger, W. Karrer, and O. Brandli. Current allergic asthma and rhinitis: diagnostic efficiency of three commonly used atopic markers (IgE, skin prick tests, and Phadiatop). Results from 8329 randomized adults from the SAPALDIA Study. Swiss Study on	Study type:Diagnostic Cross-sectional study Data source: Information from a random sample of residents (part of the SAPALIDA study) from the general population aged 18-60 yrs. Setting: General population	N = 8329 Inclusion criteria: • Aged 18-60 • Undertaken the 3 atopic tests (total IgE, SPT and Phadiatop) Exclusion criteria: • Not done the 3 atopic	Male: Female Data in another publication – ON ORDER Mean age: Data in another publication – ON ORDER Current smokers: Data in another publication – ON ORDER Dx of asthma (in N=8329): DA (DrDx): N=566, CA (current asthma): N=208, CAA (current allergic asthma): N=153, CAR (current allergic	Index test **Total IgE** • Pharmacia CAP FEIA technology **CUT-OFF:** positive = ≥100 kU/l. Index test**Specific IgE** • Phadiatop fluoroenzyme immunoassay • Allergens: ○ Pollens ○ House dust mite ○ Moulds ○ Cat – total IgE only NOT USING DATA AS RESULTS ARE COMBINED **CUT-OFF:** positive = above the reference serum value. Reference standard**Clinical Dx** Dx of current allergic asthma (by qu'aire results: CA + respiratory symptoms related to common allergy exposure in the last 12 mths asthma.	**Current allergic asthma**	Ref std +	Ref std –	Total	Source of funding: Swiss National Science Foundation and Federal Office of Education and Science. Limitations: High cut off; Unclear time between Ref standard and Index test
					Total IgE +	87	1807	1894	
					Total IgE -	66	6369	6435	
					Total	153	8176	8329	
					Sensitivity Specificity		56.9 77.9		
					PPV, NPV		4.6, 99.0		
					Current allergic asthma (all allergens)	Ref std +	Ref std –	Total	
					Sp IgE +	NR	NR	NR	
					Sp IgE -	NR	NR	NR	
					Total	NR	NR	8329	
					Sensitivity Specificity		72.5 71.9		
					PPV, NPV PLR and NLR		4.6, 99.3 -		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Air Pollution and Lung Diseases in Adults. *Allergy* 53 (6):608-613, 1998. TSCHOPP 1998	Country:Switzerland Recruitment: 1 year period	tests.	rhinitis): N=1361, CAA and/or CAR: N=1422, Phadiatop: N=2410, SPT+: N=1912, IgE+: N=1890.	Time between index test and reference standard: not reported (likely to be different time as one was based on questionnaire results). Target condition Current allergic asthma. DATA NOT GIVEN FOR DA (Dr Dx asthma).			Additional data:

G.10 FeNO for diagnosis

Table 66: BERLYNE 2000[161]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
G. S. Berlyne, K. Parameswaran, D. Kamada, A. Efthimiadis, and F. E. Hargreave. A comparison of exhaled nitric oxide and induced sputum as markers of airway inflammation. *J.Allergy Clin.Immunol.* 106 (4):638-644, 2000.	Study type: Case-control study Data source: clinic pts Setting: Chest allergy clinic pts Country: Canada Recruitment: Not reported	N = 131 adults - n=38 asthma – steroid naiive (1) - n=35 asthma – steroid Tx (2) - n=8 eosinophilic bronchitis (3) - n=28 healthy controls - atopic (4) - n=22 healthy controls – nonatopic (5) Inclusion criteria: (1): Asthma (steroid naiive). Symptoms of wheeze, breathlessness or cough in past year plus MCT PC20 <8 mg/ml if the FEV1/VC >70%; or a post-BD FEV1 >15% if the FEV1/VC was <70%. Not received ICS in previous month. (2): Asthma (steroid-Tx). As above but receiving regular ICS Tx. (3): Eosinophilic bronchitis without asthma. Cough in the past yr, FEV1/VC >80%, MCT PC20 >16 mg/ml, and induced sputum eos count >5% of total squamous cell count (above the 90th percentile for sputum eos). (4): Healthy controls - atopic. No symptoms. FEV1/VC >70% and MCT PC20 >16 mg/ml. Positive SPT to at least 1 common allergen. (5): Healthy controls -nonatopic. As	Male: Female 43%/57% Mean age: 39 years	Index test FeNO: chemiluminescence analyser; fixed flow rate 45 ml/s. Sievers 240 device. Target condition FeNO levels asthma vs. healthy vs. eosinophilic bronchitis (separately)	**Median (IQR) FeNO levels:** 1. Asthma – steroid naiive: 39 (43) ppb 2. Asthma – steroid Tx: 17 (12) ppb 3. Eosinophilic bronchitis: 65 (92) ppb 4. Healthy - atopic: 11 (6) ppb 5. Healthy - nonatopic: 9 (7) ppb - median of healthy = 10 The median FeNO was SS differenet between the groups. Median FeNO was SS higher in the group with asthma (steroid naiive) vs. healthy controls (p<0.001) Median FeNO was SS lower in the group with asthma (steroid Tx) vs. steroid naiive (p<0.001) Median FeNO was SS lower in the group with asthma (steroid Tx) vs. Eosinophilic bronchitis.	Source of funding: Not reported Limitations: - Additional data: None

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
BERLYNE 2000		above but negative SPT to at least 1 common allergen. Exclusion criteria: • Current smokers (as reduces ENO levels) • Ex-smokers <1 year • Symptoms of RTI in 4 wks before study or other complicating respiratory disease			There was NS difference in median FeNO levels between the control groups (ie. atopic status does not matter).	

Table 67: CARDINALE 2005[270]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
F.	Study type:	N = 175 children (mean 10 years)	Male: Female	Index test	**Median (IQR) FeNO levels:**	Source of

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
Cardinale, F. M. De Benedictis, V. Muggeo, P. Giordano, M. S. Loffredo, G. Iacoviello, and L. Armenio. Exhaled nitric oxide, total serum IgE and allergic sensitization in childhood asthma and allergic rhinitis. *Pediatr.Allergy Immunol.* 16 (3):236-242, 2005.	Case-control study Data source: Pts from clinic Setting: Paediatric allergy clinic Country: Italy Recruitment: No detail if consecutive. Nov 2002 - Sept 2003.	- n=109 asthma (83.4% were allergic – SPT+; 51% of all asthma had additional allergic rhinitis (1a and 1b = atopic/nonatopic asthma) - n=41 allergic rhinitis, moderate persistent (2) - n=25 healthy controls (3) Inclusion criteria: (1): mild intermittent asthma. History of symptoms, pulmonary function tests and response to inhaled beta-adrenergic agents according to international guidelines. History of at least 1 episode of asthma in past year and stable at time of study. (2): moderate persistent allergic rhinitis. Clinical history and positive SPT to common allergens. None had ever had wheezing or received asthma medication. Steriod Tx or antihistamine had to be withdrawn >3 months before study. (3): Healthy controls. Non-atopic (absence of allergic symptoms in history and negative SPT), no history of airway disease, allergy or significant medical illness and not taking any medication. Exclusion criteria:	1:2 (overall) Mean age: 10 years (overall)	FeNO: chemiluminescence analyser; flow rate 50 ml/s. NOA Tm280 Sievers device Target condition FeNO levels asthma vs. allergic rhinitis vs. healthy controls (separately)	1. All asthma: 22.7 (9.1 - 48) ppb 1a. n=91 Asthma atopic: 25.6 (11.4 – 56.2) ppb 1b. n=18 Asthma non-atopic: 11.5 (5.4 - 15.5) ppb 2. Allergic rhinitis: 15.3 (9.4 – 31.0) 3. Healthy: 5.9 (3.4 – 9.3) Asthma pts and allergic rhinitis has SS higher FeNO levels than controls (p=0.0001 and p=0.016) The mean eNO was SS higher in allergic vs. non-allergic asthma (p<0.001) There was NS difference in eNO between the non-allergic asthma pts vs. healthy controls. There was NS difference in eNO between all asthma pts vs. allergic rhinitis. The median FeNO level was SS higher in allergic asthma vs. allergic rhinitis. (p=0.03)	funding: Not reported Limitations: - Additional data: None

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
CARDINAL E 2005		History of significant medical illness, previous or current allergen hyposensitisation, history or signs of RTI in 4 wks before study, tobacco smoke exposure in the family.				

Table 68: CHATKIN 1999[304]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Chatkin JM, Ansarin K, Silkoff PE, McClean P, Gutierrez C, Zamel N et al. Exhaled	Study type: Cross-sectional observational study Data source:	N = 38 chronic cough + 23 healthy controls Inclusion criteria: Chronic cough (>3 weeks) of unknown cause referred for	Male: Female 11:27 chronic cough plus 8:15 controls Mean age: Adult: asthma:	Index test FeNO: chemiluminescence analyser (Sievers 280 device); mouth pressure 20mm Hg. Flow rate 45ml/s Optimal cut-off 30ppb		Ref std +	Ref std -	Total	Source of funding: Dr Chatkin recipient of a grant from CAPES
					Index test +	6	4	10	
					Index test -	2	26	28	
					Total	8	30	38	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables		Comments
nitric oxide as a noninvasive assessment of chronic cough. American Journal of Respiratory and Critical Care Medicine. 1999; 159(6):1810-1813. *(Guideline Ref ID CHATKIN1999)*	Data collected for this study Setting: Asthma centre (tertiary referral centre) or affiliated community respiratory clinics Country: Canada Recruitment: Not stated	diagnosis; normal CXR and FEV1 >80% predicted Exclusion criteria: Use of codeine or any other medication for chronic cough, upper respiratory infection within 4 weeks; use of corticosteroids within 6 weeks; current smoking; any significant medical conditions; contra-indications to methacholine challenge.	41 (12) yr; chronic cough non-asthma: 47 (15) yr; healthy controls: 38 (8) Non-asthma = chronic cough (mean 53.8 weeks) but methacholine negative	Reference standard Positive to methacholine challenge (PC20 ≤8mg/mL) Tests done within 24 hours Target condition Asthma diagnosis vs. chronic cough non-asthma FeNO levels asthma vs. chronic cough non-asthma or vs. healthy controls	Sensitivity Specificity	75% 87%	Limitations: None Additional data: None
					PPV NPV PLR / NLR	60% 93% 5.8 / 0.3	
					AUC	Not stated	
					Median (25th to 75th percentile) FeNO levels: asthma (chronic cough and methacholine positive): 75.0 (34.1 to 104.0) ppb n=8, p=0.0014 vs. non-asthma, p=0.007 vs. controls	Non-asthma (chronic cough and methacholine negative): 16.7 (11.0 to 21.7) ppb n=30 Healthy controls: 28.3 (23 to 30) ppb, n=23	

Table 69: CIPRANDI 2013[334]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
Giorgio	Study type:	N = 330 children (median 12 years)	Male: Female	Index test	**Median (IQR) FeNO levels:**	Source of

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
Ciprandi, Maria Angela Tosca, and Michele Capasso. High exhaled nitric oxide levels may predict bronchial reversibility in allergic children with asthma or rhinitis. *J.Asthma* 50 (1):33-38, 2013. CIPRANDI 2013	Case-control study Data source: Hospital pts Setting: Hospital Country: Italy Recruitment: Not reported	- n=180 allergic intermittent asthma (1) - n=150 allergic rhinitis (2) Inclusion criteria: (1): allergic asthma. Paediatrician using validated criteria (GINA). Consistent symptoms and signs, lung function impairment and BDR. BDR FEV1>12%. Allergy by SPT for common aeroallergens. (2): rhinitis. Paediatrician using validated criteria (GINA). Exclusion criteria: Negative SPT Acute or chronic uRTI Anatomical or nasal disorders Previous or current immunotherapy Use of CS, nasal or oral vasoconstrictors, LABA anti-leukotrienes or antihistamines in previous 4 weeks.	56%/44% Median age: (1) children 13 yrs (2) children 10 yrs	FeNO: chemiluminescence analyser; flow rate 50 ml/s. Sievers 280 device. Target condition FeNO levels allergic asthma vs. rhinitis (separately)	1. Asthma allergic: 34 (29 - 381) ppb 2. Rhinitis: 27 (21 - 35) The median FeNO was SS higher in the allergic asthma vs. rhinitis group (p<0.001)	funding: No sponsorship. Limitations: - Additional data: None

Table 70: CORDEIRO 2011[360]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Cordeiro D, Rudolphus A, Snoey E, Braunstahl GJ. Utility of nitric oxide for the diagnosis of asthma in an allergy clinic population. Allergy and Asthma Proceedings. 2011; 32(2):119-126. *(Guideline Ref ID CORDEIRO2011)*	Study type: Cross-sectional observational study Data source: Routine prospective database Setting: General outpatient allergy clinic Country: The Netherlands Recruitment: January 2007 to September 2007	N = 114 Inclusion criteria: New referrals to outpatient allergy clinic Exclusion criteria: Patients using inhaled corticosteroids or oral corticosteroids within 6 weeks	Male: Female 43: 71 Median age: Asthma: 39 (range 7-83); non-asthma 38 (7-87)	Index test FeNO: measured online at constant flow rate 50mL/s (Niox-Flex device) Optimal cut off 27ppb. Flow rate 50ml/s Reference standard History of typical respiratory symptoms and FEV1 improvement >12% and >200mL with salbutamol 400µg or PC20 histamine ≤8mg/mL Time between index test and reference standard: within 6 weeks Target condition Asthma diagnosis vs. non-asthma (Allergic rhinitis, non-allergic rhinitis, eczema, urticarial, other analysed all together); raw data calculated from sensitivity/ specificity FeNO levels: Asthma vs. Allergic rhinitis, non-allergic rhinitis, eczema, urticarial, other analysed all together Asthma vs. allergic rhinitis		Ref std +	Ref std -	Total	Source of funding: Not stated Limitations: Unclear if pts treated with asthma medication apart from corticosteroids (steroid-naiive) Additional data: None
					Index test +	33	6	39	
					Index test -	9	66	75	
					Total	42	72	114	
					Sensitivity Specificity		78% 92%		
					PPV / NPV		86% / 87%		
					AUC		0.88		
					Median (range) FeNO levels: Asthma: 44 (6-290) ppb, n=42		Non-asthma (all diagnoses): 17 (5-45) ppb, n=72 p<0.001 Allergic rhinitis only (sub-group of above): 21 ppb, n=32 p<0.001		

Table 71: DEYKIN 2002[429]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
Deykin et al., 2002. Exhaled nitric oxide as a diagnostic test for asthma: online versus offline techniques and effect of flow rate. American Journal of Respiratory and Critical Care Medicine: 165: 1597-1601 REF ID: DEYKIN2002	Study type: Prospective case-control study Data source: Collected for study Setting: Pulmonary and Critical Care Division, Department of Medicine Country: US Recruitment: Not stated	N = 62 Inclusion criteria: • Adult nonsmokers with and without asthma • Those with asthma had a history of asthma, with either a 12% improvement in FEV1 after inhalation of a beta-agonist or a methacholine PC20 of 8 mg/ml or less • Those without asthma had no history of asthma, normal spirometry, and a methacholine PC20 more than 8 mg/ml. • Free of upper respiratory infection for at least 6 weeks Exclusion criteria: Systemic or inhaled corticosteroids used within 8 weeks	Male: Female 26:36 Mean (SEM) age: People with asthma (n=34) 29.6 (1.6) Healthy (n=28) 27.3 (1.3) Medications: No asthma medications except for short-acting bronchodilators, which were withheld for at least 8 hours before all testing	Index test FeNO: chemiluminescence analyser (NOA 280 Sievers device); triplicate recordings. Target condition FeNO levels asthma vs. healthy controls	<table><tr><td></td><td>Ref std +</td><td>Ref std -</td><td>Total</td></tr><tr><td>Index test +</td><td>-</td><td>-</td><td>-</td></tr><tr><td>Index test -</td><td>-</td><td>-</td><td>-</td></tr><tr><td>Total</td><td>-</td><td>-</td><td>-</td></tr><tr><td>Sensitivity Specificity</td><td colspan="2"></td><td>- -</td></tr></table>Various flow rates reported: 50ml/s: Asthma: 57.9 (6.5) Healthy: 26.3 (2.2); (p<0.001 for comparison)	Source of funding: Supported by the National Institutes of Health (P50-HL-56383) and an educational grant from Merck USHH Limitations: Additional data: Other flow rates reported but not relevant

Table 72: FUKUHARA 2011[529]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Fukuhara et al., 2011. Validation study of asthma screening criteria based on subjective symptoms and fractional exhaled nitric oxide. Annals of Allergy, Asthma and Immunology: 107: 480-486 REF ID: FUKUHARA2011	Study type: Cross-sectional study Setting: Outpatients, Dept. of Pulmonary Medicine, University Hospital Country: Japan Recruitment: Not reported	N = 61 Adults Inclusion criteria: • At least 1 of the subjective symptoms: recurrent cough, wheezing or dyspnoea (including chest tightness) • Exclusion criteria: • Prior history of asthma • Taking oral or inhaled steroids or anti-leukotriene agents	Male: Female 31:30 Mean age (range): 55.6 (17-81) Medications: 6 current smokers and 13 former smokers	Index test FeNO level: measured using online method in accordance with American Thoracic Society/European Respiratory Society and a chemiluminescence analyser (NA623N, Chest MI, Japan). Information on the compatibility with other NO analysers provided. FeNO level measured 3 times with differences within 10%, mean of 3 measurements used. Flow rate 50ml/s. Cut-off: ≥40ppb Comparator test n/a Reference standard At least 2 of the following: induced sputum eosinophilia, airway hyperresponsiveness, reversible airway obstruction. Airway reversibility defined as a change in FEV1 of 200ml or ≥12% after short-acting β-agonist or after 2-4 weeks treatment with ICS or bronchodilator. Airway		Ref st +	Ref st -	Total	Source of funding: Not reported Limitations: • Consecutive or random recruitment not reported • 97 patients with symptoms gave consent but 36 were unable to undergo testing (reasons not reported) Additional data:
					Index test +	33	2	35	
					Index test -	9	17	26	
					Total	42	19	61	
					Sensitivity Specificity PPV NPV		78.6% 89.5% 94.3% 65.4%		
					FeNO levels, mean (95% CI), ppb Asthma 90.1 (65.9 -114.3) Non-asthma (with symptoms): 40.1 (21.8 – 58.5)				

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
				hyperresponsiveness defined as dose of MCh at which airway resistance began to rise (cut-off <12.5U). And other diseases ruled out using chest radiography, computed tomography and other lab tests. Time between index test and reference standard: FeNO measured before other pulmonary function tests <u>Target condition</u> Asthma		

Table 73: HEFFLER 2006[648]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Heffler E, Guida G, Marsico P, Bergia R, Bommarito L, Ferrero N et al.	<u>Study type:</u> Prospective study <u>Data source:</u> Collected for study	N = 48 symptomatic + 30 healthy controls <u>Inclusion criteria:</u> Patients referred to allergy department for diagnostic evaluation of	<u>Male: Female</u> 21:27 <u>Mean age:</u> Asthma: 42.33 (range 17-69) yr; non-asthma: 38.73 (11-75) yr	<u>Index test</u> FeNO: chemiluminescence analyser (Niox device); mouth pressure 10 cm H_2O; exhalation rate 50mL/s; mean of 3 recordings. Different cut offs used: optimal cut off for highest combination of		Ref std +	Ref std -	Total	<u>Source of funding:</u> Regione Peimonte-Ricerca Sanitaria Finalizzata 2003
					Index test +	14	12	26	
					Index test -	4	18	22	
					Total	18	30	48	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables		Comments
Exhaled nitric oxide as a diagnostic test for asthma in rhinitic patients with asthmatic symptoms. Respiratory Medicine. 2006; 100(11):1981-1987. *(Guideline Ref ID HEFFLER2006)*	Setting: Allergy outpatients clinic Country: Italy Recruitment: Not stated	persistent rhinitis and asthma-like lower airways symptoms (cough, dyspnoea, chest tightness and wheezing) during the last 2 months Exclusion criteria: Use of steroids or any other anti-inflammatory medications in last 2 months, current smoking (in previous 12 months), previous diagnosis of asthma, respiratory infection in last 6 weeks		sensitivity and specificity was 36ppb Reference standard Typical symptoms and significant response to bronchodilator (≥12% improvement in FEV1 with salbutamol) or airway hyper-responsiveness to methacholine (PD20 FEV1 ≤800µg) Time between index test and reference standard: same time Target condition Asthma vs. no asthma (not meeting criteria for diagnosis of asthma but final diagnoses not reported); raw data calculated from sensitivity/specificity FeNO levels: asthma vs. no asthma (symptomatic) or healthy controls	Sensitivity Specificity	77.8% 60.0%	Limitations: None Additional data: None
					PPV / NPV Accuracy	54.0% / 81.8% 66.67%	
					AUC	0.78	
					Geometric mean (95% CI) FeNO levels: asthma 59.7 (50.2 to 89.0) ppb, n=18	Non-asthma (symptomatic): 30.4 (28.1 to 45.1) ppb, n=30, p=0.001 vs. asthma Healthy controls: 12.2 (11.1 to 15.1) ppb, n=30, p<0.001 vs. asthma	

Table 74: KOSTIKAS 2008[906]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Kostikas K, Papaioannou AI, Tanou K, Koutsoker	Study type: Prospective study Data source:	N = 149 symptomatic + 70 healthy controls Inclusion criteria: Subjects with at least	Male: Female 76: 73 symptomatic + 37:33 controls	Index test FeNO: exhalation flow rate 50mL/s (NIOX MINO device) Optimal cut off 19ppb		Ref std +	Ref std -	Total	Source of funding: Not stated Limitations:

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
a A, Papala M, Gourgoulianis KI. Portable exhaled nitric oxide as a screening tool for asthma in young adults during pollen season. Chest. 2008; 133(4):906-913. *(Guideline Ref ID KOSTIKAS 2008)*	Collected for the study Setting: University students Country: Greece Recruitment: Spring 2006	one asthma symptom on a screening questionnaire among students Exclusion criteria: Previous diagnosis of asthma or rhinitis treated with anti-inflammatory medication (inhaled or nasal corticosteroids, long-acting β-agonists, leukotriene modifiers, antihistamines or methylexanthines); respiratory tract infection in past 6 weeks; recent smoking cessation (<2 months prior to study)	Mean age: Asthma: 21.6 (2.7) yr; allergic rhinitis: 21.8 (3.0) yr; non-specific symptoms: 22.1 (3.1) yr; healthy controls: 21.4 (2.3) yr	Reference standard History + significant bronchodilator reversibility, positive methacholine challenge test, or clinical or spirometric response to a 4-week trial of inhaled corticosteroids Time between index test and reference standard: same time Target condition Asthma vs. Allergic rhinitis (raw data calculated from sensitivity/ specificity) FeNO levels: Asthma vs. Allergic rhinitis or non-specific respiratory symptoms or healthy controls (separately)	Index test +				Population symptomatic but had not presented to healthcare professionals Additional data: None
					Index test -				
					Total				
					Sensitivity Specificity		Not used as calculated including healthy control group		
					PPV NPV PLR NLR				
					AUC		0.544		
					Median (IQR) FeNO levels: Asthma: 20.0 (14.0 to 31.0), n=63		Allergic rhinitis: 17.0 (12.5 to 23.0), n=57, p=0.28 vs. asthma Non-specific symptoms: 11.0 (8.5 to 12.5), n=29, p<0.0001 vs. asthma Healthy controls: 10.5 (7.0 to 13.0), n=70,		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
						p<0.0001 vs. asthma			

Table 75: KOWAL 2009[914]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Kowal K, Bodzenta-Lukaszyk A, Zukowski S. Exhaled nitric oxide in evaluation of young adults with chronic cough. Journal of Asthma 2009; 46(7):692-698. *(Guideline Ref ID KOWAL2009)*	Study type: Prospective study Data source: Collected for study Setting: Asthma clinic Country: Poland Recruitment: September 2000 to November 2006	N = 540 symptomatic + 100 healthy controls Inclusion criteria: Young adult patients with chronic cough (at least 8 weeks) referred to asthma clinic for evaluation Exclusion criteria: Use of any anti-asthma medication, treatment with angiotensin converting enzyme inhibitors, use of codeine or other cough suppressant, upper respiratory tract infection within 4 weeks before study, presence of any systemic disease, contra-indications to	Male: Female Not stated Mean age: Symptomatic: 26.5 (range 18-45) years; healthy controls: 24 (18-39) years	Index test FeNO: chemiluminescence analyser (NOA 280 Sievers device); fixed expiratory resistance 16cm H_2O; exhalation flow rate 50mL/s; mean of 3 recordings Optimal cut off 40ppb Reference standard Significant diurnal changes in PEF or significant improvement of FEV1 with 200µg salbutamol over next 6 months Time between index test and reference standard: up to 6 months Target condition Asthma vs. Rhinitis/sinusitis or gastroesophageal reflux; raw data calculated from sensitivity/ specificity FeNO levels: Asthma vs.		Ref std +	Ref std -	Total	Source of funding: Medical University of Bialystok Limitations: None Additional data: None
					Index test +	157	63	220	
					Index test -	21	299	320	
					Total	178	362	540	
					Sensitivity Specificity		88.3% 82.6%		
					PPV NPV PLR NLR		72.6% 94% 5.08 0.14		
					AUC		0.924		
					Median (95% CI) FeNO levels: asthma: 86ppb (95% CI 72 to 94.5), n=178		Rhinitis/sinusitis: 37ppb (95% CI 35.6 to 42.9), n=211, p<0.0001 Gastroesophageal reflux: 14.8ppb (95% CI 13.3 to 16.2),		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables		Comments
		bronchial histamine test; people with seasonal allergies if cough appeared in pollen season or up to 4 weeks after the season		Rhinitis/sinusitis; gastroesophageal reflux; healthy controls (separately)		n=108, p<0.0001 vs. asthma Healthy controls: 13ppb (95% CI 11 to 15), n=100, p<0.0001 vs. asthma	

Table 76: LOUHELAINEN 2008[1029]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Louhelainen N, Rytila P, Obase Y, Makela M, Haahtela T, Kinnula VL et al. The value of sputum 8-isoprostane in detecting oxidative stress in mild asthma. Journal of	Study type: Prospective study Data source: Collected for study Setting: Division of Pulmonary Medicine Country: Finland Recruitment: Not stated	N = 37 asthma + 11 COPD + 28 healthy controls Inclusion criteria: Patients with newly-diagnosed asthma (wheezing, prolonged cough and shortness of breath plus significant bronchial reversibility i.e. reduction in post-exercise PEF and/or FEV1 ≥15% or improvement in FEV1 ≥12% after bronchodilator or PD15 of histamine	Male: Female Asthma: 17:20 COPD: 7:4 Healthy controls: 11:17 Mean age: Patients with asthma and healthy controls grouped by age (adult asthma mean 38 yr, range 16-72 yrs; adult control mean 40, range 19 to 56 yr; asthma child mean 10, range	Index test FeNO: chemiluminescence analyser (Niox device); exhalation flow rate 50mL/s; mean of 3 recordings Reference standard BDR ≥12%, Exercise challenge test ≥15% or histamine challenge test PD15 <0.4mg Target condition FeNO levels: Asthma vs. healthy controls (COPD not reported)		Ref std +	Ref std -	Total	Source of funding: Finnish Tuberculosis Association Foundation, funding of the Helsinki University Hospital (EVO), the Sigrid Juselius Foundation, the Ida Montin Foundation, an unrestricted research grant from GSK
					Index test +	-	-	-	
					Index test -	-	-	-	
					Total	-	-	-	
					Sensitivity Specificity		-		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables		Comments
Asthma. 2008; 45(2):149-154. *(Guideline Ref ID LOUHELAINEN2008A)*		<0.4mg or ≥20% diurnal variation in PEF values and/or ≥15% improvement in PEF after bronchodilator at home) COPD exacerbation Healthy controls <u>Exclusion criteria:</u> Not stated	7-14 yr; healthy child mean 11, range 8-14 yrs); COPD all adult (mean 72, range 54 to 85)		PPV NPV PLR NLR	-	<u>Limitations:</u> None <u>Additional data:</u> None
					AUC	-	
					Median FeNO levels: Asthma children: 35.5ppb, n unclear – between 19 and 23 Asthma adults: 81.8ppb, n unclear – between 5 and 14	Healthy children: 11.9ppb, n unclear – between 9 and 13, p<0.001 vs. children with asthma Healthy adults: 16.6ppb, n unclear – between 6 and 15, p=0.025 vs. adults with asthma	

Table 77: SATO 2008[1499]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Sato S, Saito J, Sato Y, Ishii T, Xintao W, Tanino Y et al. Clinical usefulness of fractional exhaled nitric oxide for diagnosing prolonged cough. Respiratory Medicine. 2008; 102(10):1452-1459. *(Guideline Ref ID SATO2008)*	Study type: Prospective Data source: Collected for study Setting: Department of Pulmonary Medicine Country: Japan Recruitment: January 2004 to January 2007	N = 71 Inclusion criteria: Prolonged cough or wheezing >3 weeks attending Department of Pulmonary Medicine; age 20-78 years; no abnormalities on CXR or CT scan; no prior history of treatment for pulmonary disease; never used oral or inhaled corticosteroids Exclusion criteria: None apart from above	Male: Female Bronchial asthma: 20:10 Cough variant asthma: 7:11 Eosinophilic bronchitis without asthma: 4:4 Others: 8:7 Mean (95% CI) age: Bronchial asthma: 55.5 (48.9 to 62.5) Cough variant asthma: 48.2 (39.4 to 57.0) Eosinophilic bronchitis without asthma: 45.3 (33.3 to 57.2) Others: 55.5 (47.5 to 63.5)	Index test FeNO: chemiluminescence analyser (Device from Kimoto, Japan - no further details given); exhalation flow rate 50mL/s; mouth pressure 16 cm H_2O; mean of 3 recordings Optimal cut off 38.8ppb Reference standard Bronchial asthma (BA): cough and wheezing for 3 weeks or longer, sputum eosiniophilia and positive airway hyper-responsiveness (methacholine <12.5 units) or reversible airflow limitation (improvement in FEV1 of 200mL and ≥12% from baseline after salbutamol 200µg or long-acting β2-agonist). Cough variant asthma (CVA): As above except without wheezing Time between index test and reference standard: same time Target condition Asthma group = bronchial asthma + cough variant asthma together; compared with non-asthma group = eosinophilic bronchitis without asthma (EB), post-infectious cough, post-nasal drip, COPD, chronic bronchitis, cough		Ref std +	Ref std -	Total	Source of funding: Not stated Limitations: None Additional data: None
					Index test +	38	2	40	
					Index test -	10	21	31	
					Total	48 (BA + CVA)	23 (EB + other)	71	
					Sensitivity Specificity		79.2% 91.3%		
					Mean (95% CI) FeNO levels: Bronchial asthma: 93.5 (72.5 to 120.7) ppb, n=30, p=0.001 vs. CVA group, p<0.001 vs. EB group, p<0.001 vs. others Cough variant asthma: 46.7 (33.6 to 64.8) ppb, n=18, p<0.001 vs. EB		Eosinophilic bronchitis without asthma: 16.4 (10.9 to 24.8) ppb, n=8, NS vs. others Other = post-infectious cough, post-nasal drip, COPD, chronic bronchitis, cough with GERD or ino-bronchial syndrome: 21.2 (15.1 to 29.7) ppb, n=15	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables		Comments
				with GERD or sino-bronchial syndrome (i.e. one comparator group); raw data calculated from sensitivity/ specificity FeNO levels: Bronchial asthma and cough variant asthma (separately); compared with a) eosinophilic bronchitis without asthma, and b) other = post-infectious cough, post-nasal drip, COPD, chronic bronchitis, cough with GERD or sino-bronchial syndrome (i.e. two comparator groups)	group, p<0.001 vs. others		

Table 78: SIVAN 2009[1602]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Sivan et al., 2009. The use of exhaled nitric oxide in the diagnosis of asthma in school	Study type: Cross-sectional study Setting: Outpatient paediatric pulmonary clinic, Children's Hospital	N = 150 (113 excluding those on ICS from analysis) Children Inclusion criteria: • Non-specific respiratory symptoms suggestive of asthma for at least 3 months, including cough, wheezing and shortness of breath with or without trials of	Male: Female ~56% male Age range: 5-18yrs (mean 12) Medications: Withheld bronchodilato	Index test • FeNO Online single exhalation technique recommended by ERS/ATS guidelines Reference standard Made by paediatric pulmonologist after 18 months follow-up. Based on history of 2 or more clinical exacerbations of wheezing documented by a physician;		Ref st +	Ref st -	Total	Source of funding: Not reported Limitations: • Recruited 150 patients but excluded 37 on ICS from analysis • Time between IT
					Index test +	52	5	57	
					Index test -	17	39	56	
					Total	69	44	113	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
children. Journal of Pediatrics: 155: 211-216 REF ID: SIVAN2009	<u>Country:</u> Israel <u>Recruitment:</u> Consecutive	treatment with bronchodilators and ICS. • Follow-up for at least 1 year <u>Exclusion criteria:</u> • Symptoms of unresolved respiratory tract infection • Systemic clinical manifestations of atopy such as anaphylaxis, angioedema, food allergy, urticarial, systemic or inflammatory disease	rs for 24 hours. Unclear if on medications for 18 months between IT and RS.	dyspnoea or cough relived by bronchodilators; documented variability in FEV1 ≥15% in response to bronchodilators at any time during the follow-up period; OR documented variability in FEV1 ≥15% over time with or without controller medications (ICS or montelukast). Results of provocation tests included when available. Time between index test and reference standard: 18 months <u>Target condition</u> Asthma	Sensitivity Specificity PPV NPV	75% 89% 93% 70%			and RS = 18 months • Unclear if all had objective test with RS • Interpretation of RS not done blinded to results of spirometry IT <u>Additional data:</u>

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments

Table 79: SHIMODA 2013[1563]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Shimoda	Study type:	N = 90 cough variant	Male: Female	Index test		Ref std	Ref std	Total	Source of

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
T, Obase Y, Kishikawa R, Iwanaga T, Miyatake A, Kasayama S. The fractional exhaled nitric oxide and serum high sensitivity C-reactive protein levels in cough variant asthma and typical bronchial asthma. Allergology International. 2013; 62(2):251-257. *(Guideline*	Prospective study, case-control Data source: Collected for study Setting: Department of respiratory medicine Country: Japan Recruitment: Not stated	asthma + 92 bronchial asthma + 90 healthy controls Inclusion criteria: Both patients with cough variant asthma and bronchial asthma were to be free of attacks and newly diagnosed. The diagnoses of cough variant asthma and bronchial asthma were based on the GINA guidelines Healthy subjects had no past history of asthma, atopic diseases, or other respiratory diseases and had no current respiratory symptoms Exclusion criteria: Treated with any type of steroid; concurrent hypertension, diabetes mellitus, hyperlipidaemia;	Bronchial asthma: 44:48 Cough variant asthma: 32:58 Controls: 47:43 Mean age: Bronchial asthma: 38.6 (13.8) yr Cough variant asthma: 44.7 (14.7) yr Controls: 37.4 (11.5) yr; p=0.004 between groups Symptom duration: bronchial asthma: 6.0 (8.8) yr; cough variant asthma: 2.5 (4.4) yr, p=0.001	FeNO: chemiluminescence analyser (NOA 280 Sievers device); mouth pressure 16 cm H_2O; flow rate 50mL/s; mean of 3 recordings Cut off: n/a (case-control study for levels only) Reference standard Newly diagnosed asthma (bronchial or cough variant) using GINA guidelines: Cough variant asthma: chronic cough persisting for longer than 8 weeks but without wheezing or dyspnoea; no past history of asthma or other respiratory diseases; wheeze or rhonchi not audible on chest auscultation; BHR to inhaled acetylcholine; bronchodilators effective against their coughs; normal chest radiograph results. Bronchial asthma: history of episodic dyspnoea, wheezing and cough; at least 15% reversibility in FEV1 after inhalation of 200 µg of salbutamol and/or BHR to acetylcholine. Time between index test and reference standard: n/a Target condition Bronchial asthma vs. cough variant asthma		+	-		funding: Not stated Limitations: Patient groups not comparable at baseline Additional data: None
					Index test +				
					Index test -				
					Total				
					Sensitivity Specificity				
					Mean (SD) FeNO levels: bronchial asthma: 92.6 (85.5) ppb, n=92, p<0.001 vs. controls		Healthy controls: 18.0 (6.4) ppb, n=90 Cough variant asthma: 35.6 (43.3) ppb, n=90, p<0.001 vs. bronchial asthma, p<0.001 vs. controls		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables		Comments
Ref ID SHIMODA 2013)		cough too severe to measure bronchial hypersensitivity		FeNO levels: Each type of asthma compared separately with healthy controls.			

Table 80: SHOME 2006[1568]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Shome GP, Starnes III JD, Shearer M, Kennedy R, Way A, Arif A et al. Exhaled nitric oxide in asthma: Variability, relation to asthma severity, and peripheral blood lymphocyte cytokine expressio	Study type: Prospective study Data source: Collected for study Setting: Division of Allergy and Immunology Country: USA Recruitment: Not stated	N = 19 asthma (11 mild; 8 moderate to severe) + 17 healthy controls Inclusion criteria: Patients with newly-diagnosed asthma (symptoms, signs and spirometry according to National Heart, Lung and Blood Institute) plus increase ≥12% after albuterol 2.5mg; untreated at baseline Exclusion criteria: COPD, CF, lupus pneumonitis, sepsis, respiratory infection in previous 6 weeks, congestive heart failure, smoking,	Male: Female Not stated Mean (SEM) age: Mild asthma: 52.36 (17.10) yr; moderate to severe asthma: 38.25 (8.52) yr; controls: 38.71 (13.04) yr, mild vs. control: p<0.05	Index test FeNO: 10cm H2O resistance; flow rate 50mL/s (CLD 88sp, EcoPhysics device) Reference standard BDR ≥12% Target condition FeNO levels: asthma vs. healthy controls. Patients with asthma grouped by mild versus moderate/ severe disease		Ref std +	Ref std -	Total	Source of funding: Department of Internal Medicine, Texas Tech University Health Sciences Center Limitations: Groups not comparable at baseline Additional data: None
					Index test +	-	-	-	
					Index test -	-	-	-	
					Total	-	-		
					Sensitivity Specificity		-		
					Mean (SEM) FeNO levels: Moderate to severe asthma: 18.53 (2.00) ppb, n=8, p<0.001 vs. controls				

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
n. Journal of Asthma. 2006; 43(2):95-99. *(Guideline Ref ID SHOME2006)*		other systemic diseases with pulmonary symptoms			Mild asthma: 6.27 (3.79) ppb, n=11, NS vs. controls MEDIAN OF BOTH ASTHMA = 24.8ppb Healthy controls: 5.90 (0.90) ppb, n=17	

Table 81: VOUTILAINEN 2013[1858]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Voutilainen M, Malmberg LP, Vasankari T, Haahtela T. Exhaled nitric oxide indicates poorly athlete's asthma. Clinical Respiratory Journal. 2013; 7(4):347-	Study type: Cross-sectional observational study Setting: Allergy and asthma clinic Country: Finland Recruitment: Not stated	N = 87 (study also included a group of elite athletes N=87, not included in this review) Inclusion criteria: Sedentary patients remitted to an allergy and asthma clinic because of respiratory symptoms	Male:Female 26:61 Mean age: 23 (14-31) Medications: No subjects on ICS at the time of the study and beta-agonists withheld	Index test FeNO: measured using online single exhalation method recommended by ATS (Niox device) Cut off 30ppb. Reference standard Based on general guidelines including typical symptoms and the objective confirmation of variable airway obstruction documented in hospital records. Such evidence was based either on BDR ≥12%, PEFv ≥20%, BDR of PEF ≥15%, exercise challenge test ≥15% or BHR MCh PD20 or hist PD15 ≤0.4mg		Ref std +	Ref std -	Total	Source of funding: Supported by the Vaino and Laina Kivi foundation (study sponors did not have invlolvment in study design, collection, analysis or interpretation of data). Limitations:
					Index test +				
					Index test -				
					Total				
					Sensitivity Specificity		43% 89%		
					PPV / NPV		-		
					AUC		0.79		
					FeNO levels: Asthma: 29.7ppb Non-asthma: 14.6ppb				

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
353. (Guideline Ref ID VOUTILAINE N2013)		(cough, dyspnoea or wheeze) Exclusion criteria: History of sports at a competitive level	accordingly	Time between index test and reference standard: 1 day Target condition Asthma FeNO levels: Asthma vs. non-asthma dx (final dx not stated)	P<0.001	Random or consecutive recruitment of patients not stated Additional data: study also included a group of elite athletes N=87, not included in this review

Table 82: WOO 2012[1914]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Woo SI, Lee JH, Kim H, Kang JW, Sun YH, Hahn YS. Utility of fractional exhaled	Study type: Prospective study Data source: Collected for study Setting:	N = 245 Inclusion criteria: Children 8- 16 years old, presenting with non-specific respiratory symptoms e.g. cough, wheezing,	Male: Female Overall: 163:82 Atopic asthma: 92:37; atopic non-asthma: 42:18; non-atopic asthma: 20:18; non-atopic non-asthma: 9:9	Index test FeNO: chemiluminescence (NIOX MINO device); flow rate 50mL/s; mean of 2 values. Optimal cut off 22ppb Reference standard History + reversible airflow	Total study population	Ref std +	Ref std -	Total	Source of funding: Basic Science Research Program through the National Research Foundation of Korea funded
					Index test +	95	10	105	
					Index test -	72	68	140	
					Total	167	78	245	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
nitric oxide (F(E)NO) measurements in diagnosing asthma. Respiratory Medicine. 2012; 106(8):1103-1109. *(Guideline Ref ID WOO2012)*	Department of Paediatrics Country: Korea Recruitment: Not stated	shortness of breath, referred to paediatric outpatients for evaluation of asthma Exclusion criteria: Receiving inhaled short-acting β2 agonist in previous 8 hours; receiving regular treatment with controller medications for 3 month or more before enrolment	Mean age: Atopic asthma: 11.7 (2.4) yr; atopic non-asthma: 12.6 (2.6) yr; non-atopic asthma: 11.6 (2.7) yr; non-atopic non-asthma 11.4 (2.0) yr	obstruction (≥12% improvement in FEV1 with inhaled β-agonist) and/or airway hyper-responsiveness (methacholine PC20 ≤8mg/mL) Time between index test and reference standard: same time Target condition Asthma vs. non-asthma (not airway hyper-responsiveness (cut off for methacholine PC20 of 8mg/mL) or reversible airflow obstruction (12% improvement in FEV1 with inhaled β-agonist); final diagnoses not stated. Asthma and non-asthma groups also sub-divided by atopic vs. non-atopic	Sensitivity Specificity		56.9% 87.2%		by the Ministry of Education, Science and Technology Limitations: Unclear if treatment naive Additional data: None
					PPV NPV PLR NLR Accuracy		90.5% 48.6% 64.5%		
					AUC		0.76, p<0.001		
					Atopic only	Ref std +	Ref std -	Total	
					Index test +	93	9	102	
					Index test -	36	51	87	
					Total	129	60	189	
					Sensitivity Specificity		72.1% 85.0%		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables		Comments
					PPV NPV PLR NLR Accuracy	91.2% 58.6%	
					AUC	0.85, p<0.001	
					Geometric mean FeNO levels: asthma: 23.4 ppb (95% CI 20.9 to 26.2), n=167	Non-asthma: 12.6 ppb (95% CI 10.9 to 14.5), n=78, p<0.001 vs. asthma	
					Atopic asthma sub-group: 29.6 (26.6 to 32.8) ppb, n=129, p<0.001 vs. atopic non-asthma, non-atopic asthma and non-atopic non-asthma	Atopic non-asthma sub-group: 13.6 (11.6 to 15.9) ppb, n=60, p<0.05 vs. non-atopic asthma and non-atopic no asthma	
					Non-atopic asthma sub-group: 10.6 (8.6 to 13.0) ppb, n=38	Non-atopic non-asthma sub-group: 9.7 (7.1 to 13.3) ppb, n=18	

Table 83: ZIETKOWSKI 2006A[1957]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
Zietkowski et al., 2006. Comparison of exhaled nitric oxide measurement with conventional tests in steroid-naive asthma patients. Journal of Investigational Allergology and Clinical Immunology: 16: 239-246 REF ID: ZIETKOWSKI 2006A	Study type: Case-control study Data source: Collected for this study Setting: Medical University Country: Poland Recruitment: Not stated	N = 140 (inc. 39 healthy controls) Inclusion criteria: • Steroid-naïve patients with mild to moderate asthma (56 allergic and 45 nonallergic) • Asthma Dx according to GINA • Stable condition free from acute exacerbations and respiratory tract infections during the previous 2 months • Healthy controls had an FEV1 greater than 80% of predicted. They were free of respiratory tract infection for 2 months prior to the study and from other significant illnesses known to affect FENO measurements (smoking, nitrate-rich diet, allergic rhinitis). Exclusion criteria: • Patients with asthma who had been treated with inhaled steroids in the past • Other factors that could alter FENO—such as smoking and nitrate–rich diet, but not asthma, features of atopy, or allergic rhinitis	Male: Female 57:83 Mean () age: Allergic asthma (n=56) 32 (12) Non-allergic asthma (n=45) 40 (12) Healthy (n=39) 33.5 (15.2) Medications: Refrain from use of inhaled bronchodilators for at least 6 and 12 hours for short- and long-acting ß2-agonists, respectively	Index test FeNO: chemiluminescence analyser; measurements were performed at an expiratory flow of 50 mL/s. Repeat measurements were performed until the 3 values agreed to within 10% of the mean. The mean value of the 3 measurements was recorded Reference standard None (levels only) Target condition FeNO levels asthma vs. healthy controls	**FeNO levels** Allergic asthma: 84.0±51.4 Non-allergic asthma: 45.8±32.6 MEDIAN OF BOTH ASTHMA = 64.9ppb Healthy controls: 12.9 ±4.6 p<0.0001 for comparison	Source of funding: Not reported Limitations: Additional data:

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
		• Smokers				

G.11 Eosinophils for diagnosis

Table 84: BACKER 2002[91]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Backer V, Nepper-Christensen S, Ulrik CS, von Linstow ML, Porsbjerg C. Factors associated with asthma in young Danish adults. Ann Allergy Asthma Immunol. 2002 Aug;89(2):148-54. BACKER2002	Study type: Cross-sectional Data source: Registry Setting: General population Country: Denmark Recruitment: Children and adolescents living in the area surrounding Rigshospitalet were drawn from the civil registration list	N = 624 103 people with asthma and 521 people who do not have asthma Inclusion criteria: Children and adolescents Exclusion criteria: Not to use theophylline or antihistamine for at least 24 hours before the test, not to use astemizole for 6 weeks before testing, oral beta-2-agonist for 12 hours before the tests. Pregnant women and breast feeding mothers were excluded from	Male N=279 Female N=345 Age: 19 to 29 years Severity of asthma: Current asthma vs. those who do not have asthma. Current smokers: 35 to 53% Current anti-asthma Inhaled or oral corticosteriod Drop-outs/missing values:	Index test **Peripheral blood eosinophils** • Venous blood sample and put into a tube containing EDTA, and the number of eosinophil leukocytes was counted in billions per litre. Reference standard N/A Target condition NA	**Blood eosinophil count. (Factor associated with asthma in young adults).** Billions per litre.	**Non-asthma:** 0.19 (0.1) **versus. Asthma** 0.26 (0.2) • P<0.01 different between two groups.	Source of funding: Danish Lung Association. Glaxo Wellcome and ALK-Abello. Limitations: Overall - LOW/UNCLEAR RIK OF BIAS. Additional data Those that had asthma had higher eosinophil counts.

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
	who were born between 1969 and 1979.	the histamine challenge and pregnant women did not undergo skin prick testing.	940 were eligible; 624 participated.				

Table 85: HALVANI 2012[627]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Abolhasan Halvani, Fatemeh Tahghighi, and Hossein Hadi Nadooshan. Evaluation of correlation between airway and serum inflammatory markers in	Study type: Case-control Data source: Asthma pts from clinic – details not reported, and age and sex matched healthy controls.	N = 98 (includes 37 healthy) Inclusion criteria: • Mild to moderate persistent asthma (GINA criteria) • Non-smokers without history of RTI or exacerbation of asthma during previous 6 weeks. • Healthy: no history of smoking, heart disease or other diseases; normal pulmonary function tests.	Male: Female 55%/45% Mean age: 37.8 years. Diagnoses: • 1. Healthy controls: n=37 • 2. Asthma ICS user: n=31 • 3. Asthma non-ICS	Index test **Peripheral blood eosinophils** • Not reported. **CUT-OFF:** N/A Reference standard N/A Time between index test and reference standard:	**Population (baseline)** Healthy controls Asthma – ICS user Asthma – non-ICS user	**Eosinophils, median No./µL** **211** **402** **517**	Source of funding: None reported. Limitations: Overall - LOW/UNCLEAR RIK OF BIAS. Additional data: N/A

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
asthmatic patients. *Lung India* 29 (2):143-146, 2012. HALVANI 2012	Setting: Outpatients (secondary care). Country: Iran Recruitment: Not reported.	Exclusion criteria: • Heart disease • Diabetes • Cancer • Obesity • Systemic inflammatory disorders.	user: n=30. Current smokers: None reported. Current anti-asthma Tx: N=31 ICS users. Drop-outs/missing values: None reported.	N/A Target condition • Asthma.	• **Asthma non-ICS user group: SS more PBE than asthma ICS users and healthy controls.**		

Table 86: HUNTER 2002[713]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
C. J. Hunter, C. E. Brightling, G. Woltmann, A. J. Wardlaw, and I. D. Pavord. A comparison of	Study type: Case-control Data source: Patients attending Dept of Respiratory medicine, staff,	N = 110 (includes n=21 healthy controls) Inclusion criteria: • Asthma: consistent clinical features, symptomatic, FEV1 >65% predicted, and	Male: Female 47%:53% Mean age: 39 years (range 14-76).	Index test **Peripheral blood eosinophils** • Standard haematological techniques. **CUT-OFF:** N/A	**Population**	**Eosinophils, mean (SEM) %**	Source of funding: None reported. Limitations: Overall - LOW/UNCLEAR RIK OF BIAS.
					Healthy controls	1.9 (0.6)	
					Pseudoasthma	2.0 (0.3)	
					Asthma	4.3 (0.6)	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
the validity of different diagnostic tests in adults with asthma. *Chest* 121 (4):1051-1057, 2002. HUNTER 2002	and volunteers. <u>Setting:</u> Patients (secondary care) and general population. <u>Country:</u> UK <u>Recruitment:</u> Dates not reported.	one or more of other criteria. • Healthy controls: no symptoms suggesting past or current asthma, non-smokers. • Pseudoasthma: people referred to hospital with Dx of asthma by GP, clinical features considered atypical and symptoms not deteriorate upon withdrawal of Tx. Symptoms improved after Tx of underlying condition. <u>Exclusion criteria:</u> None reported.	<u>Diagnoses:</u> • Asthma: n=69 • Pseudoasthma: n=20 • Healthy control: n=21 <u>Current smokers:</u> 8% <u>Current anti-asthma Tx:</u> 28%. Mean Tx time = 2 years (0-29 yrs). <u>Drop-outs/missing values:</u> None reported.	<u>Reference standard</u> N/A <u>Time between index test and reference standard:</u> N/A <u>Target condition</u> • Asthma. • Physician Dx based on clinical features and tests.	**Test results for eosinophil vs. healthy controls:** • Normal range = <6.3% • sens 21% (11-31) • spec 100 **Most tests were less specific when the reference population consisted of people with pseudoasthma.**		<u>Additional data:</u> N/A

Table 87: KHAKZAD 2009[847]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
M. R. Khakzad, M. Mirsadraee,	<u>Study type:</u> Case-control	N = 62 (includes 12 healthy)	<u>Male: Female</u> 40%/60%	<u>Index test</u> **Peripheral blood**	**Population (baseline)**	**Eosinophils, median**	<u>Source of funding:</u> Islamic Azad University.

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
M. Sankian, A. Varasteh, and M. Meshkat. Is serum or sputum eosinophil cationic protein level adequate for diagnosis of mild asthma? *Iran.J.Allergy Asthma Immunol.* 8 (3):155-160, 2009. KHAKZAD 2009	Data source: Subjects with asthma and controls (no other details reported). Setting: Not reported. Country: Iran Recruitment: Not reported.	Inclusion criteria: • Asthma: history of cough, dyspnoea, wheeze and airway hyperresponsiveness; symptoms increased during nights and some seasons; Spirometry showing obstructive pattern with >12% increase with bronchodilator or PC20 <8 mg/ml. • All were new cases or pts who had withheld their drugs for a long time. • Healthy: no history of asthma or other allergic disorders; PC20 >8 mg/ml. Exclusion criteria: • Healthy people with : evidence of peripheral blood eosinophilia, abnormal chest X-ray, history of smoking, systemic or ICS usage, recent infection.	Mean age: 39.5 years (range 9-76). Diagnoses (GINA criteria): • 1. Healthy controls: n=12 • 2. Asthma Mild intermittent: n=6. • 3. Asthma mild persistent: n=16. • 4. Asthma moderate persistent: n=13 • 5. Asthma severe: n=15 Current smokers: None reported. Current anti-asthma Tx: None reported. Drop-outs/missing values: None reported.	**eosinophils** • Automated cell counter (Sysmex). **CUT-OFF:** N/A Reference standard N/A Time between index test and reference standard: N/A Target condition • Asthma.		**%**	Limitations: Overall - LOW/UNCLEAR RIK OF BIAS. Additional data: N/A
					Healthy controls	**1.2**	
					All asthma	**1.0**	
					Asthma Mild intermittent	**2.0**	
					Asthma mild persistent	**3.6**	
					Asthma moderate persistent	**3.2**	
					Asthma severe	**3.2**	
					• Asthma: SS higher PBE than healthy controls.		

Table 88: KOTANIEMI 2002[907]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Anne Kotaniemi-Syrjanen, Tiina M. Reijonen, Kaj Korhonen, and Matti Korppi. Wheezing requiring hospitalization in early childhood: predictive factors for asthma in a six-year follow-up. *Pediatr.Allergy Immunol.* 13 (6):418-425, 2002. KOTANIEMI 2002	Study type: Case series (prospective) Data source: Prospective study: 6-year follow-up of children with infection-related wheeze; data used for 6 years only to see at 6 years the % who have asthma. Setting: Outpatients (secondary care) Country: Finland Recruitment: 6 year follow-up data January to March 1999 (original baseline study December 1992-1993)	N = 82 (**FINAL Dx: N=33 asthma; N=49 non-asthma)** Inclusion criteria: • Children from previous study who were available for follow-up. Exclusion criteria: None reported.	Male: Female 74%:26% Median age: 7.2 (5.6 - 8.8 years) Current smokers: N/A Current anti-asthma Tx: 30/33 asthma pts used cromones (n=18) or inhaled steroids (n=12) for maintenance medication for asthma. Drop-outs/missing values: N=18 from the original 100	Index test **Peripheral blood eosinophils** • Method not reported. **CUT-OFF:** ≥0.45 x 10^9/l. Reference standard **Clinical Dx – clinical history and questionnaire (symptoms), and exercise challenge test** (pulmonary testing before and after exercise using flow-volume spirometry and FEV_1 – positive = auscultatory wheezing post-exercise and/or ≥15% fall in FEV_1). **Asthma diagnosed if:** 1. On continuous maintenance Tx-asthma 2. suffered from repeated (≥2) episodes of wheezing and/or prolonged cough (≥4 wks) apart from infection during previous 12 months reported by parents. 3. positive exercise challenge test. **Non-Asthma diagnosed if:** wheezing or prolonged cough but negative exercise challenge OR positive exercise test but no asthma symptoms. Time between index test and reference standard: unclear Target condition: Asthma.	**Population** False positives: 8, false negatives: 15, true positives: 18, true negatives: 41 Sensitivity: 18/33 Specificity: 41/49 PPV: 18/26 (69% reported in the paper) NPV: 41/56	**% with Eosinophil counts ≥0.45 x 10^9/l**	Source of funding: Ida Montin Foundation, Kerttu and kale Viik Fund, Kuopio University Hospital. Limitations: Overall - LOW/UNCLEAR RIK OF BIAS. Additional data: N/A

Table 89: KROEGEL 1998[920]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
C. Kroegel, M. Schuler, M. Forster, R. Braun, and P. R. Grahmann. Evidence for eosinophil activation in bronchiectasis unrelated to cystic fibrosis and bronchopulmonary aspergillosis: discrepancy between blood eosinophil counts and serum eosinophil cationic protein levels. *Thorax* 53 (6):498-500, 1998. KROEGEL 1998	Study type: Case-control Data source: Consecutive pts with bronchiectasis, plus age and sex matched control groups (allergic asthma, COPD and healthy). Setting: Secondary care. Country: Germany Recruitment: Jan 1992 – August 1994.	N = 56 (n=14 asthma) Inclusion criteria: • Proven or new bronchiectasis (persistent cough, recurrent pneumonias and frequent haemoptysis, large quantities of partially foul purulent sputum production, positive sputum cultures>3 years, and radiological evidence of bronchiectasis) • COPD or asthma (diagnostic criteria previously published) • All pts without clinical signs of current infectiou exacerbation in previous 4 weeks • Healthy controls – no pulmonary disease. • No family history of similar lung disease. Exclusion criteria: • None reported.	Male: Female N=8/N=6 Mean age: 54.8 years (range 31-78). Diagnoses: • 1. Healthy controls: n=14 • 2. Bronchiectasis: n=14 • 3. COPD: n=14 • 4. Allergic asthma: n=14. Current smokers: None reported. Current anti-asthma Tx: Not reported. Drop-outs/missing values: None reported.	Index test **Peripheral blood eosinophils** • Standard cytometry. **CUT-OFF:** N/A Reference standard N/A Time between index test and reference standard: N/A Target condition • Allergic asthma.	**Population (baseline)**	**Eosinophils, median x10^7/l**	Source of funding: County of Thuringia, Germany. Limitations: Overall - LOW/UNCLEAR RIK OF BIAS. Additional data: N/A
					Healthy controls	**10.1 (range 1.6-21.4)**	
					Bronchiectasis	**10.2 (1.0-32.0)**	
					COPD	**11.7 (range 0.6-31.5)**	
					Allergic asthma	**30.5 (range 12.3-69.3)**	
					• **Allergic asthma: SS more PBE than all other groups** • **NS difference in PBE count between bronchiectasis and healthy controls or COPD.**		

Table 90: LABBE 2001[943]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
A. Labbe, B. Aublet-Cuvelier, L. Jouaville, G. Beaugeon, L. Fiani, I. Petit, L. Ouchchane, and M. Doly. Prospective longitudinal study of urinary eosinophil protein X in children with asthma and chronic cough. *Pediatr.Pulmonol.* 31 (5):354-362, 2001. LABBE 2001	Study type: Case-control Data source: Children seen in outpts by paediatric pulmonologist. Setting: Outpatients (secondary care). Country: France Recruitment: Feb 1997-March 1999.	N = 143 (N=88 asthma, N=22 severe) Inclusion criteria: • Asthma: a) recent onset, not receiving any Tx except B-2 agonists if needed. b) severe asthma, taking ICS regularly for at least 12 months. • Healthy: admitted to dept for non-infectious, non-respiratory disorder. No history of asthma or atopic disease. • Chronic cough: referred for chronic cough (>3months duration/year), or recurrent cough (>3 episodes/year, each lasting >15 days). Experienced no episodes of wheezing or dyspnoea. Exclusion criteria: • None reported.	Male: Female 64%/36% Mean age: 7.0 years (range 1.1 - 16.5). Diagnoses (GINA criteria): • 1. Healthy controls: n=34. • 2. Chronic cough: n=21. • 3. Asthma: n=88 Current smokers: N/A. Current anti-asthma Tx: Some pts. Drop-outs/missing values: None reported.	Index test **Peripheral blood eosinophils** • Method not reported. **CUT-OFF:** N/A Reference standard N/A Time between index test and reference standard: N/A Target condition • Asthma.	**Population (baseline)**	**Eosinophils, median** x10^9/L	Source of funding: Pharmacia. Limitations: Overall - LOW/UNCLEAR RIK OF BIAS. Additional data: N/A
					Healthy controls	**0.25**	
					Chronic cough	**0.21**	
					Asthma	**0.40**	
					• Asthma: SS higher PBE than healthy controls and chronic cough groups (p<0.01).		

Table 91: METSO 2000[1127]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Metso T, Kilpiö K, Björkstén F, Kiviranta K, Haahtela T. Detection and treatment of early asthma. Allergy. 2000 May;55(5):505-9. METSO 2000	Study type: Case-control study (pt groups within this were randomly assigned to Tx groups for 6 weeks)). Data source: Hospital staff recruited patients Setting: Hospital Country: Finland Recruitment: 80 consecutive patients	N = 190 (N=30 control and N=160 asthma – N=39 budesonide, N=39 terbutaline). Inclusion criteria: Subjective symptoms for <1 year. At least one of the following lung-function test outside the reference range: FEV1 improvement >15% after inhaled beta2 agonist PEF diurnal variation >15% and PEF increase of >15% after inhaled beta2-agonist at least once during a 2 week period Exclusion criteria: treatment with anti-inflammatory medication, lung diseases other than asthma, and respiratory tract infection in the previous 4 weeks. Past and present long-term respiratory diseases including asthma, respiratory tract infections and preceding 4 weeks and hyper responsiveness to histamine.	Male: Female Budesonide 32/7 Terbutaline 31/10 Controls 28/2 Age: 16-60 Severity of asthma: Mild/Moderate Budesonide 31/8 Terbutaline 30/11 Controls 0/0 Current smokers: Budesonide 14 Terbutaline 9 Controls 0 Current a-asthma Tx: Drop-outs/missing values: NA	Index test **Peripheral blood eosinophils** **CUT-OFF:** NA Reference standard N/A Target condition NA	**Blood eosinophils 10^9/L**	**Control:** 0.13 **Budesonide group:** **Pre-Tx:**0.20 **Post-Tx (6 wks):** 0.11** **Terbutaline group** **Pre-Tx:** 0.16 **Post-Tx (6 wks):** 0.14 **Post-Tx (6 wks terbutaline + 2 ks budesonide):** 0.12** ** p<0.05 vs baseline	Source of funding: Research institute of Helsinki University Central Hospital and the Finnish Allergy Research Foundation. Limitations: Overall - LOW/UNCLEAR RIK OF BIAS. Additional data: N/A

Table 92: NORDLUND 2012[1245]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Nordlund B, Konradsen JR, Kull I, Borres MP, Önell A, Hedlin G, Grönlund H. IgE antibodies to animal-derived lipocalin, kallikrein and secretoglobin are markers of bronchial inflammation in severe childhood asthma. Allergy. 2012 May;67(5):661-9. NORDLUND 2012	Study type: Case-series Data source: Hospital based paediatric clinics Setting: Outpatients (secondary care) Country: Denmark Recruitment: Hospital based paediatric clinics	N = 39 (mild to moderate) Inclusion criteria: Children from 7 to 18 years of age with diagnosed asthma according to the Global initiative for asthma (GINA). At least 6months of regular treatment with ICS, min 800 microgram of budesonide or equivalent for problematic severe asthma and 100-400 microgram budesonide or equivalent for children with mild to moderate asthma. Physician diagnosed asthma. Exclusion criteria: children with lung or neurological diseases, as well as those born prematurely (gestational age <36 weeks) were excluded.	Male:female 59: 41 Age: 13.8±2.9 years Severity of asthma: Controlled mild to moderate. And severe patients were included. Current smokers: 35 to 53% Current anti-asthma Inhaled or oral corticosteriod Drop-outs/missing values: Unclera	Index test **Peripheral blood eosinophils** • Venous blood sample and the number of eosinophil were measured. Reference standard N/A Target condition NA	**Blood count of eosinophils (10^9 x 1^{-1}, mean SD)**	• Mild to moderate asthma 0.25± 0.19	Source of funding: Freemason Child House Foundation Swedish Asthma and Allergy Associations Research Fund and Swedish Heart and Lung Foundation Limitations: Overall - LOW/UNCLEAR RIK OF BIAS. Additional data: N/A

Table 93: PIIPPOSAVOLAINEN 2007[1344]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
E Piippo-Savolainen, S Remes, and M Korppi. Does blood eosinophilia in wheezing infants predict later asthma? A prospective 18-20-year follow-up. *Allergy Asthma Proc.* 28 (2):163-169, 2007. PIIPPOSAVOLAINEN 2007	Study type: Case-series (prospective) Data source: Infants hospitalised for bronchiolitis. Setting: Hospital (secondary care). Country: Finland. Recruitment: 1981-1982.	N = 83 Inclusion criteria: • Infants (<2 years) hospitalised for broncholitis • Bronchiolitis: respiratory wheezing and/or prolonged expirum during lower respiratory infection. Exclusion criteria: None reported.	Male: Female Not reported. Mean age: <2 years (mean or range not given). Diagnoses: N/A at baseline. Current smokers: N/A Current anti-asthma Tx: Not reported. Drop-outs/missing values: None reported.	Index test **Peripheral blood eosinophils** • Fuchs-Rosenthal counting chamber. **CUT-OFF:** N/A Reference standard N/A Time between index test and reference standard: N/A Target condition • Asthma	**BASELINE VALUES Population: wheezing**	**Eosinophils, median (25th-75th percentile)** **counts**	Source of funding: None reported. Limitations: Overall - LOW/UNCLEAR RIK OF BIAS. Additional data: N/A
					Wheezing (all 83 pts)	0.1×10^9/L (0.028 – 0.321)	

Table 94: POPOVIC 2002[1367]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
S. Popovic-Grle, M. Mehulic, F. Pavicic, I. Babic, and Z. Beg-Zec. Clinical validation of bronchial hyperresponsiveness, allergy tests and lung function in the diagnosis of asthma in persons with dyspnea. *Coll.Antropol.* 26 Suppl:119-127, 2002. POPOVIC 2002	<u>Study type:</u> Diagnostic Cross-sectional study <u>Data source:</u> Outpatients with dyspnoea, treated for breathlessness; referred by GP due to suspected asthma. <u>Setting:</u> Outpatients (secondary care) <u>Country:</u> Croatia <u>Recruitment:</u> Not reported	N =195 (**FINAL Dx:** N=141 asthma, N=17 COPD, N=29 rhinitis/sinusitis, N=8 unsolved so further examined) <u>Inclusion criteria:</u> • Outpatients treated for breathlessness <u>Exclusion criteria:</u> • None reported.	**ASTHMA pts** <u>Male: Female</u> 48%:52% <u>Mean age:</u> 39 years <u>Current smokers:</u> 20% <u>Current anti-asthma Tx:</u> Not mentioned <u>Drop-outs/missing values:</u> None	<u>Index test</u> **Peripheral blood eosinophils** • Method not mentioned **CUT-OFF:** positive = not reported. <u>Reference standard</u> **Physician Dx (pulmonologist)** Based on questionnaire (medical history of occasional asthma attacks with wheezing and nocturnal wakening due to dyspnoea), and on the basis of bronchodilation test (reversible obstruction) with salbutamol. Time between index test and reference standard: unclear <u>Target condition</u> Asthma. N=141 were people with diagnosed asthma.	**Asthma**	Ref std +	Ref std –	Total	<u>Source of funding:</u> Not reported. <u>Limitations:</u> Overall - LOW/UNCLEAR RIK OF BIAS. <u>Additional data:</u> N/A
					Eosin +	21	33	54	
					Eosin -	120	21	141	
					Total	141	54	195	
					Sensitivity Specificity		15% (21/141) 39% (21/54)		
					PPV NPV PLR and NLR		64% (21/33) 74% (120/162) -		
					AUC		-		
					% eosinophils in asthma pts, mean (SD)		Not reported		

Table 95: POSTMA 1995[1370]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
D. S. Postma and M. D. Lebowitz. Persistence and new onset of asthma and chronic bronchitis evaluated longitudinally in a community population sample of adults. *Arch.Intern. Med.* 155 (13):1393-1399, 1995. POSTMA 1995	Study type: Diagnostic Cross-sectional study Data source: Adults from an epidemiologic study of obstructive airway disease. Setting: General population Country: USA Recruitment: Original study: 1972-1985	N =2169 (N=2130 had Dx data) (**FINAL Dx:** N=345 any asthma, N=303 emphysema and/or chronic bronchitis, N=124 Low 1st FEV1, N=1358 none) Inclusion criteria: Age ≥20 years Exclusion criteria: None reported.	**Reported in a separate publication (Lebowitz 1989)** Male: Female - Mean age: Adults (details not reported) Current smokers: - Current anti-asthma Tx: - Drop-outs/missing values: -	Index test **Peripheral blood eosinophils** Stained slides counted from the 1st and 6th surveys. **CUT-OFF:** eosinophilia (positive) = ≥5% 1st survey, or ≥3% 6th survey. Based on distribution of all values in either survey. R eference standard **Physician Dx** Based on questionnaire (symptoms) and clinical evaluations (including FVC, and reversibility of airways obstruction (FEV1 before and after 5 mins after inhalation of 2 puffs of isoproterenol hydrochloride from a metered dose inhaler. Time between index test and reference standard: unclear Target condition Asthma. N=345 were people with diagnosed asthma.	**Asthma**	Ref std +	Ref std –	Total	Source of funding: Dutch Asthma fund and National Heart, Lung and Blod Institute, USA. Limitations: Overall - LOW/UNCLEAR RIK OF BIAS. Additional data: N/A
					Eosin +	103	-	-	
					Eosin -	242	-	-	
					Total	345	1989	2130	
					Sensitivity Specificity		30% (103/345) -		
					PPV NPV PLR and NLR		- - -		
					AUC		-		
					% eosinophils in asthma pts, mean (SD)		Not reported		

Table 96: RYTILA 2000[1481]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
P. Rytila, T. Metso, K. Heikkinen, P. Saarelainen, I. J. Helenius, and T. Haahtela. Airway inflammation in patients with symptoms suggesting asthma but with normal lung function. *Eur.Respir.J.* 16 (5):824-830, 2000. RYTILA 2000	Study type: Case-control Data source: Consecutive pts with respiratory symptoms, and healthy controls. Setting: Outpatients (secondary care). Country: Finland Recruitment: Oct 1996-March 1997.	N = 68 (includes n=43 healthy controls) Inclusion criteria: • Pts with respiratory symptoms suggestive of asthma. • At least 2/6 respiratory symptoms for >2 months and <1 year. • Healthy – no respiratory symptoms or history of chronic pulmonary diseases. Exclusion criteria: • Pts treated with a-inflammatory asthma medication. • Pts or healthy pple who had clinically diagnosed respiratory infection 8 wks before study. • Pts who had used histamine H2 blockers.	Male: Female 41%: 59% Mean age: 37.7 years (range 15-75). Diagnoses: • 1. Healthy controls (normal lung function tests): n=43 • 2. Respiratory symptoms (no significant airflow variability, and not hyperresponsive): n=36 • 3. Asthma (FEV1 increase ≥12% 15 mins after SABA, or PEF varied by >12% from morning to evening for ≥3 days during 2-week follow-up. Had increased bronchial responsiveness to inhaled histamine): n=25 Current smokers: 31% Current anti-asthma Tx: Not reported. Drop-outs/missing values: None reported.	Index test **Peripheral blood eosinophils** • Method not reported. **CUT-OFF:** N/A Reference standard N/A Time between index test and reference standard: N/A Target condition • Asthma.	**Population (baseline)** Healthy controls Respiratory Symptoms Asthma Atopic asthma Non-atopic asthma • **Asthma: SS more PBE than respiratory symptom pts (p=0.002) and healthy pple (p<0.0001).** • **Respiratory symptoms: SS more PBE than healthy pple (p=0.01).** • **Atopic asthma: SS more PBE than non-atopic asthma pts p=0.04)**	**Eosinophilsmean x10^9/l** **0.11** **0.17** **0.41** 0.51 0.27	Source of funding: None reported. Limitations: Overall - LOW/UNCLEAR RIK OF BIAS. Additional data: N/A

Table 97: SHIELDS 1999[1562]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Shields MD, Brown V, Stevenson EC, Fitch PS, Schock BC, Turner G, Taylor R, Ennis M. Serum eosinophilic cationic protein and blood eosinophil counts for the prediction of the presence of airways inflammation in children with wheezing. Clin Exp Allergy. 1999 Oct;29(10):1382-9. SHIELDS1999	Study type: Cross sectional study Data source: Wheezing children undergoing an elective surgical procedure for a non-inflammatory condition at the Hospital Setting: Hospital Country: Northern Ireland Recruitment: -	N = 137 Inclusion criteria: • History of wheezing in the previous year • Free from recent respiratory infection. Exclusion criteria: Alternative causes of wheezing.	Male N=48 Female N=29 Age: 1-15 years (mean not reported) Severity of asthma: Atopic asthma Current smokers: N/A Current anti-asthma Tx: 43 were taking anti-inflammatory therapy, however there was no effect on blood eosinophil counts. Drop-outs/missing values:	Index test **blood eosinophils** • Blood sample taken pre-surgery. Eosinophil counts obtained from blood smears by routine methods. **CUTOFF positive** = 4% and 8% (elevated). Reference standard **Physican Dx** Detailed asthma and allergy history. Diagnoses: 1. Atopic asthma – symptoms triggered by known aeroallergens, who had other personal atopic features, strong family background of atopy or elevated serum IgE compared to normal values. 2. Viral-associated wheezing – no personal or family background of atopy, wheezing predominantly in winter and solely in association with viral upper RTI. Target condition Asthma (N=60 atopic asthma diagnosed).	**Blood eosinophil %** **Area under curve for predicting airways inflammation** **Blood eosinophils** **>4%** **>8%**	**All patients** N=77 4 (0-25) **People with atopic asthma** n=60 4.10 (1-25) **Log serum ECP concentration** = 0.75 **Log blood eosinophil %** = 0.76 **>4%** **Sensitivity** 62% **Specificity** 67% **PPV %** 56% **PLR** 1.9 **>8%** **Sensitivity** 38% **Specificity** 93% **PPV %** 78% **PLR** 5.4	Source of funding: National Asthma Campaign and the Northern Ireland Chest Heart and Stroke Association. Limitations: Overall - LOW/UNCLEAR RIK OF BIAS. Additional data: Serum eosinophil percentages in BAL and blood were lowest (NS) when last symptoms occurred more than 12 weeks previously

Table 98: SILVESTRI 2001A[1583]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes		Comments
M. Silvestri, F. Sabatini, D. Spallarossa, L. Fregonese, E. Battistini, M. G. Biraghi, and G. A. Rossi. Exhaled nitric oxide levels in non-allergic and allergic mono- or polysensitised children with asthma. *Thorax* 56 (11):857-862, 2001. SILVESTRI 2001A	Study type: Case-control Data source: Children with asthma referred to outpatient department. Setting: Outpatients (secondary care) Country: Italy Recruitment: Dates not reported.	N = 112 (N=26 additional healthy controls, but data not given). Inclusion criteria: • Children • History of mild asthma • Positive response to methacholine challenge • Stable clinical condition • Not taken inhaled steroids at least in the year before the study Exclusion criteria: None reported.	Male: Female 58%:42% Mean age (SD): 10.6 (0.3), range 0-18 years. Types of asthma: • Non-allergic: n=56 • Sensitised: n=56 ○ Monosensitised (dust mites): n=23 ○ Polysensitised (dust mites and at least one other allergen class): n=33 Current smokers: N/A Current anti-asthma Tx: None reported. Drop-outs/missing values: None reported.	Index test **Peripheral blood eosinophils** • Technicon H6000. **CUT-OFF:** N/A Reference standard N/A Time between index test and reference standard: N/A Target condition Asthma.	**Population: asthma**	**Eosinophils, % and median (IQR)**		Source of funding: None reported. Limitations: Overall - LOW/UNCLEAR RIK OF BIAS. Additional data: N/A
						%	**Cells/mm³**	
					All allergic	7.5 (5.0-11.8)	500 (370-855)	
					Mono-sensitised	6.9 (5.3-13.7)	500 (370-893)	
					Poly-sensitised	8.3 (4.9-10.0)	500 (263-750)	
					Non-allergic	2.5 (1.6-4.2)	125 (100-300)	
					Children with allergic asthma had SS higher blood eosinophilia - % and absolute numbers: • median difference %: 4.6, 95% CI 3.2-5.9; p=0.0001 • median difference cells/mm³: 375, 95% CI 237.9 – 512.1, p=0.0001 **There was NS difference between mono- and poly-sensitised children (p>0.1).**			

Table 99: SILVESTRI 2003[1586]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
M Silvestri, F Sabatini, R Sale, AC Defilippi, L Fregonese, E Battistini, MG Biraghi, and GA Rossi. Correlations between exhaled nitric oxide levels, blood eosinophilia, and airway obstruction reversibility in childhood asthma are detectable only in atopic individuals. *Pediatr.Pulmonol.* 35 (5):358-363, 2003. SILVESTRI 2003	Study type: Case-control Data source: Children with atopic asthma and age/gender matched children with non-atopic asthma referred to outpatient department. Setting: Outpatients (secondary care) Country: Italy Recruitment: Dates not reported.	N = 92 Inclusion criteria: • Children • History of mild asthma • Atopic or non-atopic • Not have upper or lower RTIs 2 months before study • Not taken anti-asthma Tx (except for β_2-agonists as necessary – which were avoided 12hrs before study). Exclusion criteria: None reported.	Male: Female 65%:35% Mean age (SD): 10.7 (0.3) years. Types of asthma: • Atopic: n=66 • Non-atopic: n=26 Current smokers: N/A Current anti-asthma Tx: None reported. Drop-outs/missing values: None reported.	Index test **Peripheral blood eosinophils** • Technicon H6000. **CUT-OFF:** N/A Reference standard N/A Time between index test and reference standard: N/A Target condition • Asthma. • Atopic/non-atopic diagnosed according to SPT to common aeroallergens (those sensitised to pollen were tested outside of the pollen season)	**Population: asthma**	**% eosinophils, Median (IQR)** **%**	Source of funding: None reported. Limitations: Overall - LOW/UNCLEAR RIK OF BIAS. Additional data: N/A
					All	5.5 (3.0-9.8)	
					Atopic	6.7 (4.6-10.7)	
					Non-atopic	3.0 (1.8-4.3)	
					Children with atopic asthma had SS higher blood eosinophilia than non-atopic (p=0.001). **Within the atopic group, there was NS difference between mono- and poly-sensitised children (p>0.05).**		

Table 100: TILEMANN 2011[1737]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
L Tilemann, L Gindner, F Meyer, J Szecsenyi, and A Schneider. Differences in local and systemic inflammatory markers in patients with obstructive airways disease. *Prim.care respir.j.* 20 (4):407-414, 2011. TILEMANN 2011	Study type: Diagnostic Cross-sectional study Data source: Consecutive pts with suspected obstructive airways disease (OAD). Setting: Primary care Country: Germany Recruitment: Dates not mentioned.	N = 210 (**FINAL Dx:** N=86 asthma, N=36 COPD, N=13 partial reversibility, N=75 No OAD) Inclusion criteria: • Pts presenting for first time to GP with complaints suggestive of OAD • Symptoms: dyspnoea, coughing and/or expectoration persisting for at least 2 months. Exclusion criteria: • Respiratory tract infections in the previous 6 weeks • Well-known contraindications for bronchodilator reversibility testing or bronchial provocation – pregnancy, untreated hyperthyroidism, unstable coronary artery disease, and cardiac arrhythmia.	Male: Female 45%:55% Mean age: 49 years Current smokers: 39% Current anti-asthma Tx: 5.2% (inhaled corticosteroids) Drop-outs/missing values: • Eosinophils: N=13 • FeNO: N=54 Pts were instructed not to use any bronchodilator or inhaled steroid and to stop smoking 12 hrs before assessments.	Index test **Peripheral blood eosinophils** • Flow cytometry (ADVIA system) **OPTIMAL CUT-OFF:** positive = 4.15%. Reference standard **Bronchodilation test (salbutamol)** Pts with FEV^1 <80% predicted received BDT with additional whole body plethysmography 20 mins after inhaling 400µg salbutamol. If no obstruction in the first lung function test, a BPT with methacholine was performed. Diagnoses: • COPD (irreversible OAD): FEV1 <12% and <200mL compared to baseline,). • Asthma: (fully reversible OAD): reversibility in FEV1 >12% and >200mL	**Asthma**	Ref std +	Ref std –	Total	Source of funding: Federal Ministry of Education and Research, Germany. Limitations: Overall - LOW/UNCLEAR RIK OF BIAS. Additional data: N/A
					Eosin + ≥4.15%	-	-	-	
					Eosin - ≥4.15%	-	-	-	
					Total	86	124	210	
					Sensitivity Specificity		36% 83%		
					PPV NPV PLR and NLR		59% 65% -		
					AUC		0.602 (95% CI 0.50–0.68)		
					% eosinophils in asthma pts, mean (SD)		4.1 (3.1); 95% CI 3.3-4.7. Median 3.2		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
				compared to baseline). Time between index test and reference standard: unclear <u>Target condition</u> Asthma. N=86 were diagnosed with asthma.			

Table 101: TOMASIAKLOZOWSKA 2012[1751]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
MM Tomasiak-Lozowska, Z Zietkowski, K Przeslaw, M Tomasiak, R Skiepko, and A Bodzenta-Lukaszyk. Inflammatory markers and	<u>Study type:</u> Case-control <u>Data source:</u> Pts and healthy volunteers. <u>Setting:</u> Not	110 (N=91 asthma) <u>Inclusion criteria:</u> • Asthma (mild allergic – all atopic and sensitised to common inhaled allergens by SPT). • Healthy controls:	<u>Male: Female:</u> 50%/50% <u>Mean age:</u> 38 years <u>Current smokers:</u> None. <u>Diagnoses (GINA criteria):</u> • 1. Healthy controls: n=19. • 2. Stable* asthma, steroid naïve (no ICS Tx in past 3 mths): n=22. • 3. Stable* asthma, ICS Tx (mild to	<u>Index test</u> **Peripheral blood eosinophils** • Haematologic analyser (Coulter). **CUT-OFF:** N/A	**Population (baseline)** Healthy controls Stable asthma (no ICS)	**Eosinophils, mean** cells/mm^3 **32.0** **29.5**	<u>Source of funding:</u> Grant number given but details not specified. <u>Limitations:</u> Overall - LOW/UNCLEAR

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
acid-base equilibrium in exhaled breath condensate of stable and unstable asthma patients. *Int.Arch.Allergy Immunol.* 159 (2):121-129, 2012. TOMASIAKLOZOWSKA 2012	reported. <u>Country:</u> Poland. <u>Recruitment:</u> Not reported.	free of RTIs within past 3 months and other significant illness known to affect FeNO mmmts. <u>Exclusion criteria:</u> • Asthma exacerbation • Respiratory disease • Concomitant heart, renal, liver or collagen disease • RTI in the mouth.	moderate, low to medium ICS dose at constant dose for ≥3 mths): n=35. • 4. Severe, unstable asthma, ICS Tx (required ≥1 hospitalisations for asthma and >3 oral steroid bursts in previous year. Taking high doses of ICS and LABA ≥6 mths): n=34. *stable asthma = minimal need for rescue medication (SABA), no exacerbations and no use of systemic steroids in past 12 mths. <u>Current anti-asthma Tx:</u> Mild to moderate asthma pts had been Tx with constant low to medium doses of ICS for ≥3 mths. <u>Drop-outs/missing values:</u> None reported.	<u>Reference standard</u> N/A <u>Time between index test and reference standard:</u> N/A <u>Target condition</u> • Asthma.	Stable asthma (ICS)	**42.4**	RIK OF BIAS. <u>Additional data:</u> N/A
					Unstable asthma (ICS)	**49.8**	
					No other details of results reported for eosinophil counts.		

Table 102: TUCHINDA 1987[1777]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
M. Tuchinda, S. Habananada, J. Vareenil, N. Srimaruta,	<u>Study type:</u> Case series (prospective) <u>Data source:</u>	N = 1000 measured for blood eosinophils (N=2000 whole study)	<u>Male: Female</u> 61%:39% <u>Age:</u> <13 years	<u>Index test</u> **Peripheral blood eosinophils** • Method not reported. **CUT-OFF:** Not reported.	**Eosinophil counts (cells/mm^3)**	**%**	<u>Source of funding:</u> None reported.
					0 - 500	39.8	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
and K. Piromrat. Asthma in Thai children: a study of 2000 cases. *Ann.Allergy* 59 (3):207-211, 1987. TUCHINDA 1987	Prospective study of 2000 children with asthma Setting: Outpatients (secondary care) Country: Thailand Recruitment: December 1972-1985	Inclusion criteria: • Age <13 years • Diagnosis of bronchial asthma. Exclusion criteria: None reported.	Severity of asthma: • Mild: 29% • Moderate: 61% • Severe: 9.6% Current smokers: N/A Current anti-asthma Tx: 7% previous CS treatment; and 23% had been hospitalised with asthma. Drop-outs/missing values: Not reported	Reference standard : N/A Time between index test and reference standard: unclear Target condition Asthma. 63% of pts had other allergic diseases.	501 - 1000 1001 - 1500 1501 - 2000 >2000	29.4 15.7 8.6 6.5	Limitations: Overall - LOW/UNCLEAR RIK OF BIAS. Additional data: N/A

Table 103: VILA-INDURAIN 1999[1844]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
B. Vila-Indurain, F. Munoz-Lopez, and M. Martin-	Study type: Case-control Data source:	N = 57 (includes n=21 healthy controls)	Male: Female Not reported. Mean age:	Index test **Peripheral blood eosinophils** • Flow cytometry.	**Population (baseline – pre BPT)** Healthy controls	**Eosinophils, mean (SD)** **Cells/mm³** 161 (77)	Source of funding: None reported. Limitations:

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Mateos. Evaluation of blood eosinophilia and the eosinophil cationic protein (ECP) in the serum of asthmatic children with varying degree of severity. *Allergol.Immunopathol.(Madr).* 27 (6):304-308, 1999. VILA-INDURAIN 1999	Selection of children with asthma and control healthy children. Setting: Not reported. Country: Spain Recruitment: Dates not reported.	Inclusion criteria: • Children age 8-18 years with asthma or healthy controls. Exclusion criteria: None reported.	Range 8-18 years. Diagnoses: • 1. Healthy controls (negative allergy and respiratory function tests): n=21 • 2. Asthma (favourably evolving, with normal FEV_1): n=19 • 3. Asthma (below normal FEV_1 that normalised with salbutamol): n=13 • 4. Asthma (below normal FEV_1 that did not recover after bronchodialtion test): n=14 Current smokers: N/A Current anti-asthma Tx: Not reported. Drop-outs/missing values: None reported.	**CUT-OFF:** N/A Reference standard N/A Time between index test and reference standard: N/A Target condition • Asthma.	1. Asthma – normal FEV_1	509 (311)	Overall - LOW/UNCLEAR RIK OF BIAS. Additional data: N/A
					2. Asthma – below normal FEV_1 normalised with SABA	397 (230)	
					3. Asthma – below normal FEV_1 not normalise after SABA	319 (152)	

Table 104: ZIETKOWSKI 2006A[1957]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Z. Zietkowski,	Study type:	140 (N=101 asthma)	Male: Female	Index test	**Population**	**Eosinophils,**	Source of

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
A. Bodzenta-Lukaszyk, M. M. Tomasiak, R. Skiepko, and M. Szmitkowski. Comparison of exhaled nitric oxide measurement with conventional tests in steroid-naive asthma patients. *J.Investig.Allergol.Clin.Immunol.* 16 (4):239-246, 2006. ZIETKOWSKI 2006A	Case-control Data source: Asthma pts and healthy volunteers. Setting: Not reported. Country: Poland. Recruitment: Not reported.	Inclusion criteria: • Asthma: stable condition, free from acute exacerbations and RTIs in previous 2 mths. • Healthy: FEV1 > 80% predicted. Free of RTIs for 2 mths before study and from other significant illnesses known to affect FeNO mmts. Exclusion criteria: • Factors that could alter FeNO (such as smoking and nitrate rich diet, but not asthma) • Features of atopy or allergic rhinitis • Tx with ICS in the past.	41%/59% Mean age: 35.2 years. Diagnoses (GINA criteria and history of symptoms and SPT for allergic rhinitis): • 1. Healthy controls: n=39. • 2. Allergic asthma: n=56. • 3. Non-allergic asthma: n=45. Current smokers: Not reported. Current anti-asthma Tx: Prior to study, pts allowed to take SABA and LABA. Drop-outs/missing values: None reported.	**Peripheral blood eosinophils** • Haematologic analyser (Coulter). **CUT-OFF:** N/A Reference standard N/A Time between index test and reference standard: N/A Target condition • Asthma.	**(baseline)** Healthy controls Allergic asthma Non-allergic asthma • Asthma: SS higher PBE than healthy controls (P<0.05) • Allergic asthma: NS higher PBE than non-allergic asthma.	**mean** cells/mm^3 **119** **247** **211**	funding: None reported. Limitations: Overall - LOW/UNCLEAR RIK OF BIAS. Additional data: N/A

G.12 Histamine and methacholine challenge tests for diagnosis

Table 105: ANDERSON 2009[48]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Anderson et al. 2009. Comparison of mannitol and methacholine to predict exercise-induced bronchoconstriction and a clinical diagnosis of asthma. Resp Res 10: 4.	Study type: Diagnostic cross sectional study Recruitment: Not mentioned	N = 391 (16 not included in PP analysis reported N=375) Adults and children/youngpeople. Sn/sp given for: • all ages • <18 yrs only Inclusion criteria: Aged 6-50 yrs (BMI<35) with signs and symptoms suggestive of asthma according to the NIH questionnaire. • At least step 1 symptoms according to the NAEPPII asthma severity grading (symptoms ≤2 times per week; asymptomatic between exacerbations; exacerbations of only a few hrs to a few days; night time symptoms ≤2 times	Male: Female 182/193 Mean age: 24.3 (10.2) range 6-50 Children n=96 Adults n=279 Medications: Withholding periods of medications summarised in table in paper for inhaled agents, oral BD, CS, other medications, foods, strenuous exercise and tobacco.	Index test MCT – methacholine (Provocholine, CA) delivered from a nebulizer (DeVilbiss 646) by the dosimeter method. Concentrations were 0.0312, 0.0625, 0.125, 0.25, 0.5, 1, 2, 4, 8, 16mg/ml administered (each conc required 5 inhalations and spirometry performed within 3 minutes). PC20 calculated Cut-off: 16mg/ml Comparator test Mannitol: mannitol test kit as per standard protocol (Aridol or Osmohale Pharmaxis Ltd). FEV1 measured 60s after each dose: 0, 5, 10, 20, 40, 80, 160, 160, 160mg). 60s after the 0mg capsule, the FEV1 was measured in duplicate at the highest value taken as baseline. PD15 calculated Cut-off: ≥15% fall in FEV1 ≤635mg		Ref std +	Ref std -	Total	Source of funding: Phase III clinical trial funded by Pharmaxis Ltd and involved in the design and statistics Limitations: • Indirect population: reported ages 6-50 yrs together. Children reported separately but age 6-18, not age 5-16 as in protocol. • Not all patients included in analysis. • Consecutive or random patient selection not reported.
					Index test +	122	34	156	
					Index test -	118	101	219	
					Total	240	135	375	
					Sensitivity Specificity		50.8% 74.8%		
					PPV NPV		78.2% 46.1%		
						Mann +	Mann -	Total	
					Index test +	104	52	156	
					Index test -	64	155	219	
					Total	168	207	375	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
		per month) • FEV1 ≥70% predicted at screening Exclusion criteria: • Firm diagnosis of asthma or an exclusion of the Dx of asthma • Other pulmonary disease • Smoked >1 cigarette per week in the past yr or a ≥10pack year smoking history • Respiratory tract infection within the last 4 weeks • Skin test positive to aeroallergens present in the environment during enrolment or reported worsening symptoms when exposed to these during the study • Dx at screening visit as definitively having asthma (95-100% likelihood) or not having asthma (0-5% likelihood) • Abnormal chest x-ray or ECG		or 10% fall between consecutive doses. Reference standard Clinical Dx with objective test: made by respiratory physician at visit 5 with access to data on exercise challenge, history, examination, skin tests and BDR but not methacholine and mannitol challenge tests. Time between index test and reference standard: unclear Target condition Asthma	Sensitivity 62% Specificity 75% PPV 66.7% NPV 70.8% **Children <18 yrs (n=115)** MCT vs reference standard • Sensitivity = 66.2% • Specificity = 62.9%	• Unclear time between IT and RS Additional data: Consisted of 5 study visits. Objective tests performed on first visit and physician assigned one of 6 asthma likelihood – those with 5-95% likelihood included. Visit 2 and 3 confirmed spirometry at screening and an exercise test. Visit 4 and 5 was randomised crossover of either mannitol or methacholine. Likelihood of asthma determined again after visit 5 – but Dx of asthma for ref standard determined by physician blinded to challenge tests.

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
		• Failure to observe washout of medications				

Table 106: HEDMAN 1998[647]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Hedman et al. 1998. A rapid dosimetric methacholine challenge in asthma diagnostic: a clinical study of 230 patients with dyspnoea, wheezing or a cough of unknown cause.	Study type: Diagnostic cross sectional study Setting: Hospital pulmonary department Country: Finland Recruitment: Consecutive patients tested with the MCT from May to Sept 1994	N = 230 Adults Inclusion criteria: Referred due to dyspnoea, wheezing or a cough of unknown cause Exclusion criteria: Previous asthma Dx; use of inhaled steroids during the preceding 4 weeks FEV1 of at least 65% before challenge test and no respiratory infection during previous 4 weeks.	Male: Female 90/140 Mean age: 44.3 (16) Current smokers n=39 Medications: - Beta2-agonist used by 58% patients with a positive MCT and 32% of patients with a negative MCT - anticholinergic drug used by 5% patients with a	Index test RAPID dosimetric MCT performed with a pocket turbine spirometer (MicroSpirometer, Micro Medical Instruments). An automatic, inhalation synchronised dosimeter jet nebuliser (Spira Elektro 2, Respiratory Care Centre, Finland)used for MCh delivery. After nebulisation of 33g isotonic saline, MCh delivered in four doses 80, 400, 1700, 6900µg. FEV1 measured 90s after each dose. The concentrations were 2.5, 10, 40 and 160 mg/ml. PD20 calculated Cut-off PD20≤6900µg Comparator test None		Ref std +	Ref std -	Total	Source of funding: Not reported Limitations: • Unclear time between IT and RS Additional data:
					Index test +	47	31	78	
					Index test -	14	138	152	
					Total	61	169	230	
					Sensitivity Specificity		77.0% 81.7%		
					PPV NPV PLR NLR		60.3% 90.8%		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables		Comments
Resp Med 92: 32-39.			positive MCT and 21% of patients with a negative MCT No use of beta2-agonists for 12hrs prior to MCT, or any other asthma or antihistamine drug for 48hrs (terfenadine for 1 week and astemitsole for 4 weeks)	<u>Reference standard</u> Physician Dx with objective test (according to guidelines of the American Thoracic Society). The person who classified the patients as having or not having asthma was blinded to MCT results. Patients had to have a documented variation in FEV or PEF of 15% or greater after medication, or repeatedly a 20% or greater spontaneous daily variation in PEF monitoring during a period of 2 weeks. In addition, a 15% or greater decrease in FEV, after a specific allergen provocation or during an exercise test was a criterion for diagnosing bronchial asthma. Time between index test and reference standard: unclear <u>Target condition</u> Bronchial asthma	AUC		

Table 107: KOSKELA 2003 [905]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Koskela et al.	<u>Study type:</u>	N=42	<u>Male: Female</u>	<u>Index test</u>	PD15 ≤1mg/ml	Ref std +	Ref std -	Total	<u>Source of funding:</u>

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Responsiveness to three bronchial provocation tests in patients with asthma. Chest 2003: 124(6):2171.	Comparative test vs test study Data source: Setting: Outpatient clinic Country: Finland Recruitment: Consecutive patients with a new diagnosis of asthma over an 18 month period	Consecutive patients with a new Dx of asthma over a 18 month period Inclusion criteria: Asthma Dx based on patient history and clinical examination, including objective evidence of reversible airway obstruction (postitive exercise challenge; BDR; PEFV or PEF improvement with BD) according to the Finnish Social Insurance Institute criteria. Exclusion criteria: Previous usage of inhaled or oral CS; febrile respiratory tract infection within 4 weeks; FEV1<50% predicted; if staff physician considered COPD the most probable diagnosis.	21/16 Mean age: 49 (44-54) Current smokers n=6 Medications: subjects refrained from taking short-acting beta2-agonists for 6 hrs, inhaled anti-cholinergic drugs for 8 hrs, and theophylline for 24 hrs prior to HCT.	HCT – administered using Spiro Elektro 2 dosimeter nebuliser (Respiratory Care Centre, Finland) . Nebulisation time 0.4s, set to start 100ms after beginning of inspiration. Starting dose 25µg with 4-fold increases until the FEV1 fallen by 15% or max dose of 1600µg administered Cut-off: PD15 ≤1mg and PD15 ≤0.4mg Reference standard Mannitol – spray dried powder packed in gelatin capsules containing 5, 10, 20 and 40mg (inhaled in doubling doses up to 160mg and repeated 3 times using an Inhalator). Test until 15% fall in FEV1 or cumulative dose of 635mg reached Cut-off: >15% fall in FEV1 regardless of dose Time between index test and reference standard: 2 days to 2 weeks. Target condition Asthma (with +ve mannitol	Index test +	19	11	30	Not reported Limitations: Comparator test used as reference standard as all people had asthma Additional data: Mannitol, cold air and histamine tests given in random order within 2 weeks and at least 2 days before challenges (within 3 weeks of asthma Dx).
					Index test -	0	7	7	
					Total	19	18	37	
					Sensitivity Specificity		100% 38.9%		
					PPV NPV		63.3% 100%		
					PD15 ≤0.4mg/ml	Ref std +	Ref std -	Total	
					Index test +	16	2	18	
					Index test -	3	16	19	
					Total	19	18	37	
					Sensitivity Specificity PPV NPV		84.2% 88.9% 88.9% 84.2%		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables		Comments
				response)			

Table 108: KOWAL 2009[914]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Kowal et al. Exhaled Nitric Oxide in Evaluation of Young Adults with Chronic Cough. 2009. Journal of Asthma 46: 692-698.	Study type: Diagnostic cross sectional study Data source: (if it comes from records for instance) Setting: Asthma Clinic Country: Poland Recruitment: Patients referred by family doctors to the clinic between Sept 2000	N = 540 Inclusion criteria: Patients referred to the asthma clinic for evaluation of chronic cough Non smokers with non-productive cough of at least 8 weeks in duration, no abnormalitiy on chest radiograph and baseline lung function within normal limits Exclusion criteria: Use of anti-asthma medication before the study; treatment with ACE inhibitors; use of codeine or other cough	Male: Female Mean age: 26.5 range 18-45 years Other Dx made were rhinitis; GERD	Index test HCT – doubling concentrations of histamine (aerosol generated using a DeVilbis 646 nebuliser attached to a Rosenthal French dosimeter). Five inspiratory capacity breaths of each conc. FEV1 measured 90s after each fifth inhalation. Starting at 0.62mg/ml until 20% decrease or concentration of 32mg/ml reached. Cut-off: 8mg/ml Comparator test FENO Reference standard Significant diurnal changes in PEF or significant improvement of FEV1 on administration of 200µg of		Ref std +	Ref std -	Total	Source of funding: Limitations: • Consecutive or random patient selection not reported • RS 6 months after IT • Unclear if reference standard performed without knowledge of the results of the Index test Additional data: Data provided on a healthy
					Index test +	166	0	166	
					Index test -	12	362	374	
					Total	178	362	540	
					Sensitivity Specificity		93.3% 100%		
					PPV NPV PLR NLR		100% 96.8%		
					AUC				

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables		Comments
	and Nov2006	suppressant; upper respiratory tract infection within 4 weeks of the study; presence of any systemic disease; contradictions to HCT.		salbutamol according to the Global Initiative of Asthma (GINA) guidelines. Time between index test and reference standard: 6 months (observed for 6 months after HCT before Dx) <u>Target condition</u> Bronchial asthma			control group but not included here for calculation of sn/sp

Table 109: NIEMINEN 1992[1229]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Nieminen M.M. Unimodal Distribution of Bronchial Hyperresponsiveness to Methacholine in Asthmatic Patients. Chest: 102 (5): 1537-	<u>Study type:</u> Diagnostic cross sectional study <u>Data source:</u> <u>Setting:</u> Pulmonary Department, University Hospital	N = 791 Adults <u>Inclusion criteria:</u> dyspnoea, wheezing, prolonged cough, or a history of asthma. referred to the clinic and tested with methacholine challenge <u>Exclusion criteria:</u>	<u>Male: Female</u> 319/472 <u>Mean age:</u> 43.2 (SD 14.0) 179 current smokers Oral beta-agonists and inhaled anti-cholinergic drugs were withheld for 12	<u>Index test</u> MCT performed using a dosimeter technique with tidal breathing. An automatic, inhalation synchronised dosimeter jet nebuliser (Spira Elektro 2, Respiratory Care Centre, Finland) used for MCh delivery. Nebulisation time 0.5s, set to start 100ms after beginning of inspiration. After nebulisation of saline, MCh delivered in five cumulative doses of 18, 72, 270, 810, and 2,600 µg (concentration of MCh was 2.5 mg/ml for the doses 18 to 270µg and 25 mg/ml		Ref std +	Ref std -	Total	<u>Source of funding:</u> Supported by a grant from Suomen Astra Ltd. <u>Limitations:</u> • Unclear if reference standard performed without knowledge of
					Index test +	283	114	397	
					Index test -	36	358	394	
					Total	319	472	791	
					Sensitivity Specificity		88.7% 75.8%		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables		Comments
1543	Country: Finland Recruitment: consecutive patients referred to pulmonary department with respiratory symptoms. March 1988 – Sept 1989		hours, inhaled beta-agonists for 8 hours and theophylline compounds for 48 hours before the MCT	for the doses 810 to 2,600µg). FEV1 PD20 calculated Cut-off: 2,600µg Comparator test None Reference standard Clinical Dx according to the guidelines defined by the American Thoracic Society, a typical history with chronic or repeated symptoms, and a documented variation in FEV1 or in PEFR of more than 15 percent after medication, or repeatedly 20 percent spontaneous daily variation in PEFR monitoring during a period of two weeks. In addition, a 15 percent decrease in air flow after specific allergen provocation or in an exercise test was a criterion for diagnosing bronchial asthma. Time between index test and reference standard: unlcear Target condition Bronchial asthma	PPV NPV PLR NLR	71.3% 90.9%	the results of the Index test. • Unclear time between IT and RS Additional data: Data provided on a healthy control group but not included here for calculation of sn/sp
					AUC		

Table 110: POPOVIC 2012[1367]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Popovic-Grle et al., 2002. Clinical validation of bronchial hyperresponsiveness, allergy tests and lung function in the diagnosis of asthma in persons with dyspnea. Collegium Antropologicum: 26 Suppl: 119-127 REF ID: POPOVIC 2002	Study type: Cross-sectional study Setting: Outpatient department, University Hospital Country: Croatia Recruitment: Random	N = 195 Adults Inclusion criteria: • Referred by GP with suspected asthma and symptoms of breathlessness / dyspnoea. Exclusion criteria: • Serious diseases of other organ systems or the lungs (apart from those of an obstructive and/or allergic nature)	Male, % 51% of those given an asthma Dx Mean age: 36.5 (6.2) in those given an asthma Dx (n=141) Medications: Not reported	Index test Methacholine Challenge test (initial concentration of 0.03mg/ml, increased by doubling concentrations to 8mg/ml) Cut-off: 8mg/ml suggested as highest concentration given Comparator test n/a Reference standard Dx made on the basis of questionnaire, with typicalmedical history data of occasional asthma attacks with wheezing and nocturnal awakening because of dyspnoea, and reversible bronchial obstruction after salbutamol test (no further details stated) Time between index test and reference standard: same time Target condition		Ref st +	Ref st -	Total	Source of funding: Not reported Limitations: • Details of reference standard objective test not given • Unclear if RS results interpreted without knowledge of the IT results • Unclear if IT results interpreted without knowledge of the RS results (but objective) • Value reported in text for positive MCT result do not match other
					Index test +	137	9	146	
					Index test -	4	45	49	
					Total	141	54	195	
					Sensitivity Specificity PPV NPV		97.2% 83.3% 93.8% 91.8%		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
				Asthma					results Additional data:

G.13 Mannitol challenge test for diagnosis

Table 111: ANDERSON 2009[48]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Anderson et al. 2009. Comparison of mannitol and	Study type: Diagnostic cross sectional study	N = 391 (16 not included in PP analysis reported N=375) Adults and children/youngpeo	Male: Female 182/193 Mean age: 24.3 (10.2) range 6-50	Index test Mannitol: mannitol test kit as per standard protocol (Aridol or Osmohale Pharmaxis Ltd). FEV1 measured 60s after each dose: 0, 5, 10, 20, 40, 80, 160, 160, 160mg). 60s after the 0mg capsule, the		Ref std +	Ref std -	Total	Source of funding: Phase III clinical trial funded by Pharmaxis Ltd and involved in the design and
					Index test +	134	34	168	
					Index test -	106	101	207	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
methacholine to predict exercise-induced bronchoconstriction and a clinical diagnosis of asthma. Resp Res 10: 4.[48]	Recruitment: Not mentioned	ple. Sn/sp given for: • all ages • <18 yrs only Inclusion criteria: Aged 6-50 yrs (BMI<35) with signs and symptoms suggestive of asthma according to the NIH questionnaire. • At least step 1 symptoms according to the NAEPPII asthma severity grading (symptoms ≤2 times per week; asymptomatic between exacerbations; exacerbations of only a few hrs to a few days; night time symptoms ≤2 times per month) • FEV1 ≥70% predicted at screening Exclusion criteria: • Firm diagnosis of asthma or an	Children n=96 Adults n=279 Medications: Withholding periods of medications summarised in table in paper for inhaled agents, oral BD, CS, other medications, foods, strenuous exercise and tobacco.	FEV1 was measured in duplicate at the highest value taken as baseline. PD15 calculated Cut-off: ≥15% fall in FEV1 ≤635mg or 10% fall between consecutive doses. Comparator test Exercise: running on a treadmill whilst breathing medical grade dry air to 80-90% predicted HR (220-age) and sustained for 6 minutes. FEV1 measured 5, 10, 15 and 30 mins after and % fall in FEV1 calculated by subtracting lowest value after exercise from pre-exercise value Cut-off: positive if fall in FEV1 ≥10% Reference standard Clinical Dx with objective test: made by respiratory physician at visit 5 with access to data on exercise challenge, history, examination, skin tests and BDR but not mannitol challenge tests. Time between index test and reference standard: unclear	Total	240	135	375	statistics Limitations: • Indirect population: reported ages 6-50 yrs together. Children reported separately but age 6-18, not age 5-16 as in protocol. • Not all patients included in analysis. • Consecutive or random patient selection not reported. • Unclear time between IT and RS Additional data: Consisted of 5 study visits. Objective tests performed on
					Sensitivity Specificity PPV NPV		55.8% 74.8% 79.8% 48.8%		
						Ex +	Ex -	Total	
					Index test +	95	73	168	
					Index test -	68	136	204	
					Total	163	209	372	
					Sensitivity Specificity PPV NPV		58.6% 65.2% 56.5% 66.7%		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
		exclusion of the Dx of asthma • Other pulmonary disease • Smoked >1 cigarette per week in the past yr or a ≥10pack year smoking history • Respiratory tract infection within the last 4 weeks • Skin test positive to aeroallergens present in the environment during enrolment or reported worsening symptoms when exposed to these during the study • Dx at screening visit as definitively having asthma (95-100% likelihood) or not having asthma (0-5% likelihood) • Abnormal chest x-ray or ECG • Failure to observe washout of		<u>Target condition</u> Asthma	**Children <18 yrs (n=115)** Mannitol vs reference standard • Sensitivity = 63.2% • Specificity = 81.4% Mannitol vs Exercise • Sensitivity = 60.1% • Specificity = 58.5%	first visit and physician assigned one of 6 asthma likelihood – those with 5-95% likelihood included. Visit 2 and 3 confirmed spirometry at screening and an exercise test. Visit 4 and 5 was randomised crossover of either mannitol or methacholine. Likelihood of asthma determined again after visit 5 – but Dx of asthma for ref standard determined by physician blinded to challenge tests.

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
		medications				

G.14 Exercise challenge test for diagnosis

Table 112: AVITAL2000[81]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Exercise, methacholine, and adenosine 5'-monophosphate challenges in children with asthma: relation to severity of the disease.	Study type: Diagnostic Cross-sectional study Data source: Paediatric pulmonology clinic Setting: Secondary care Country:	N = 135 Inclusion criteria: • American Thoracic Society definition of asthma; Exclusion criteria: Upper or lower respiratory tract infection in last 4 weeks	Male: Female Not stated Mean age: 12.4 (3.9) range 6 to 25 years	Index test Exercise test 6 minute treadmill **CUT-OFF:** positive = minimum fall in FEV1 of 8.2% Reference standard **Clinical Dx** Methacholine challenge (PC20 ≤8mg/mL) Time between index test and reference standard: within 30 days Target condition Asthma	**Asthma**	Ref std +	Ref std –	Total	Source of funding: Not stated Limitations: None Additional data: None
					Exercise +	95	1	96	
					Exercise -	37	2	39	
					Total	132	3	135	
					Sensitivity Specificity		72% 67%		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Pediatric Pulmonology: 30: 207-214 Avital A, Godfrey S, and Springer C 2000. REF ID: **AVITAL2000.**	Israel Recruitment: Not stated						

Table 113: EGGLESTON1979[464]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
A comparison of the asthmatic response to methacholine and exercise. Journal of Allergy and Clinical Immunology: 63: 104-110	Study type: Diagnostic Cross-sectional study Data source: University School of Medicine Setting: Secondary care	N = 45 Inclusion criteria: • Young adults with asthma Exclusion criteria: None given	Male: Female 27:18 Mean age: Range 16 to 30 years	Index test Exercise test 5 minutes treadmill **CUT-OFF:** positive = ΔFEV1 ≥18% (cut off for 2SD from mean normal response) Reference standard **Clinical Dx** Methacholine Time between index test and reference standard: same time Target condition	**Asthma**	Ref std +	Ref std –	Total	Source of funding: Not stated Limitations: No patients were methacholine-negative so specificity cannot be calculated Additional data: None
					Exercise +	36	0	36	
					Exercise -	9	0	9	
					Total	45	0	45	
					Sensitivity Specificity		80% Not estimable		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Eggleston PA 1979. REF ID: **EGGLESTON1979**.	Country: USA Recruitment: Not stated			Asthma			

Table 114: KERSTEN2009[844]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Kersten ETG et al. Mannitol and exercise challenge tests in asthmatic children. Pediatric Pulmonology 2009; 44: 655-661. KERSTEN2009	Study type: Diagnostic Cross-sectional study Data source: Outpatients Setting: Secondary care Country: The Netherlands Recruitment:	N = 25 Inclusion criteria: • Children with a history of allergic asthma and exercise induced bronchoconstriction recruited from outpatient clinic; clinically stable, otherwise healthy; FEV1 at least 70% predicted normal value; able to run on treadmill and perform reproducible spirometry	Male: Female 17: 8 Mean age: Mean 12.4 (2.0) years	Index test Exercise challenge running with nose clip on treadmill in cold air at ice ring (temperature 1°C) for 6 minutes **CUT-OFF:** positive = ΔFEV1%init >15% for both tests Reference standard Mannitol challenge up to cumulative dose 6.35mg Time between index test and reference standard: within 4 weeks Target condition Asthma	**Asthma**	Ref std +	Ref std –	Total	Source of funding: Pediatric Research Foundation Enschede, The Netherlands Limitations: None Additional data: None
					Cold air exercise +	9	1	10	
					Cold air exercise -	4	11	15	
					Total	13	12	25	
					Sensitivity Specificity		69% 92%		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
	Not stated	<u>Exclusion criteria:</u> None given					

Table 115: KLEPACPULANIC2004[877]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Exercise and allergic diseases. Arhiv Za Higijenu Rada i Toksikologiju: 55: 197-204 Klepac-Pulanic T, Macan J, Plavec D, and Kanceljak-Macan B 2004. REF ID: **KLEPACPULANIC2004**.	<u>Study type:</u> Diagnostic Cross-sectional study <u>Data source:</u> Institute for Medical Research and Occupational Health <u>Setting:</u> Secondary care <u>Country:</u> Croatia <u>Recruitment:</u>	N = 35 <u>Inclusion criteria:</u> • GINA definition of asthma; asthma symptoms and/or taking asthma medication; all positive to histamine; all met EAACI definition of allergic asthma and had positive skin prick tests to at least 1 inhalatory allergen. Allergic rhinitis patients met EAACI definition; negative to histamine; positive skin prick tests to at least 1	<u>Male: Female</u> Not stated <u>Mean age:</u> Asthma: range 15 to 48 years; allergic rhinitis: range 15 to 45 years	<u>Index test</u> Exercise test (6 minute treadmill) **CUT-OFF:** positive = ΔFEV1 ≥10% <u>Reference standard</u> **Clinical Dx** GINA definition of asthma; asthma symptoms and/or taking asthma medication; all positive to histamine; all met EAACI definition of allergic asthma and had positive skin prick tests to at least 1 inhalatory allergen. Allergic rhinitis patients met EAACI definition; negative to histamine; positive skin prick tests to at least 1 inhalatory allergen Time between index test and reference standard: same time <u>Target condition</u>	**Asthma**	Ref std +	Ref std –	Total	<u>Source of funding:</u> Not stated <u>Limitations:</u> None <u>Additional data:</u> None
					Exercise +	5	0	5	
					Exercise -	14	16	30	
					Total	19	16	35	
					Sensitivity Specificity		26% 100%		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
	Not stated	inhalatory allergen Exclusion criteria: Exercise test or histamine challenge contra-indicated; upper respiratory viral infection within 3 weeks		Asthma			

Table 116: LIN1991[1006]

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
A bronchial response comparison of exercise and methacholine in asthmatic subjects. Journal of Asthma: 28: 31-40 Lin CC, Wu JL, Huang WC, and	Study type: Diagnostic Cross-sectional study Data source: Department of Internal Medicine Chest section Setting: Secondary care Country:	N = 22 Inclusion criteria: • People with stable unmedicated asthma; FEV1 >75% normal Exclusion criteria: None given	Male: Female 12:10 Mean age: Range 20 to 40 years	Index test Exercise test (10 minute treadmill) **CUT-OFF:** positive = ΔFEV1%init >20% Reference standard **Clinical Dx** Methacholine challenge Time between index test and reference standard: Up to 3 weeks Target condition Asthma	**Asthma**	Ref std +	Ref std –	Total	Source of funding: The National Science Council of China Limitations: None Additional data: None
					Exercise +	9	0	9	
					Exercise -	12	1	13	
					Total	21	1	13	
					Sensitivity Specificity		43% 100%		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Lin CY 1991. REF ID: **LIN1991**.	Taiwan Recruitment: July 1985 to December 1988						

G.15 Questionnaires to monitor asthma control

Table 117: MEER 2009[1797,1803]

Study (subsidiary papers)	SMASHING trial: Van 2009[1797,1803] (Van der meer 2010[1114])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=200)
Countries and setting	Conducted in Netherlands; Setting: GP and outpatient clinic, multicentre
Line of therapy	Mixed line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Physician Dx asthma, coded according to International Classification of Primary Care
Stratum	Adults and young people overall: Asthma patients 18- 50 years with ICS prescription, not receiving OCS
Subgroup analysis within study	Not stratified but pre-specified: Level of baseline control
Inclusion criteria	age 18-50 years; prescription of ICS for at least 3 months in the previous year; no serious cormorbid conditions interfering with asthma treatment; access to the internet at home; Dutch language.
Exclusion criteria	Receiving maintenance OCS treatment.
Recruitment/selection of patients	September 2005 to September 2006

Age, gender and ethnicity	Age - Range: 18-50 years. Gender (M:F): 61/139. Ethnicity:
Further population details	1. Education level: Moderate/high level of education (>50% with high education level). 2. Language: Non English speaking (Dutch speaking).
Extra comments	Baseline data: age mean (range): Monitoring 36 (19-50); UC 37 (18-50); FEV1%pred Monitoring 88 (34-133); UC 90 (53-118); AQLQ Monitoring 5.73 (3.66-6.94); UC 5.79 (3.03-7.00); ACQ Monitoring 1.12 (0.07-3.22); UC 1.11 (0-3.86); ICS 100%; ICS/LABA 60%.
Indirectness of population	No indirectness
Interventions	(n=101) Intervention 1: Monitoring asthma control + treatment - Monitoring control questionnaires + treatment. Weekly completion of electronic ACQ and instant feedback of asthma control along with advice on how to adjust treatment according to predefined algorithm and treatment plan (treatment steps according to GINA). - Four consecutive scores ≤0.5 : decrease treatment according to plan- Two scores >0.5 but <1: increase treatment according to plan- One score ≥1 but <1.5: immediately increase according to plan- One score >1.5: immediately increase treatment and contact nurse.. Duration 12 months. Concurrent medication/care: Intervention group only - online education, face-to-face group education (two 60 min sessions) and web communications with an asthma nurseBoth groups received a prior basic education session about core information on asthma, action of medications and inhaler technique instructions. All trained to measure FEV1 daily and report highest value of 3 measurements before medications. Reported daytime and nightime symptoms and ACQ weekly. No feedback provided on ACQ or lung function. Further details: 1. Additional education training : Additional education in both groups 2. Duration of study: >= 6 months (n=99) Intervention 2: Usual care. Asthma care according to Dutch guidelines (based on GINA), recommend medical review and treatment adjustment every 2 to 4 weeks in unstable asthma and once or twice yearly for controlled asthma. Control patients had access to the part of the website on which a diary of symptoms and exacerbations was kept, but not ACQ.. Duration 12 months. Concurrent medication/care: Both groups received a prior basic education session about core information on asthma, action of medications and inhaler technique instructions. All trained to measure FEV1 daily and report highest value of 3 measurements before medications. Reported daytime and nightime symptoms and ACQ weekly. No feedback provided on ACQ or lung function. Further details: 1. Additional education training : Additional education in both groups 2. Duration of study: >= 6 months
Funding	Academic or government funding (Netherlands organisation for health research and development, ZonMw, and Netherland Asthma Foundation)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ONGOING MANAGEMENT BASED ON ACQ SCORE versus USUAL CARE	

Protocol outcome 1: Quality of life at End of treatment - Actual outcome for Adults and young people overall: AQLQ at 12 months; MD 0.38 (95%CI 0.2 to 0.56) (P<0.001) AQLQ 1-7 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Exacerbation (need for OCS) at End of treatment - Actual outcome for Adults and young people overall: Emergency treatment, hospitalisation or OCS course at 12 months; HR 1.18 (95%CI 0.51 to 2.74) Reported; Risk of bias: High; Indirectness of outcome: Serious indirectness Protocol outcome 3: Asthma control questionnaires at End of Treatment - Actual outcome for Adults and young people overall: ACQ at 12 months; MD -0.47 (95%CI -0.64 to -0.3) (P<0.001) ACQ 0-6 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people with uncontrolled asthma: ACQ at 12 months; MD -0.82 (95%CI -1.1 to 0.55) ACQ 0-6 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 4: Dose of regular asthma treatment (SABA, ICS) at End of Treatment - Actual outcome for Adults and young people overall: Mean daily ICS use, µg at 12 months; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people with controlled asthma: Mean daily ICS use, µg at 12 months; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people with uncontrolled asthma: Mean daily ICS use, µg at 12 months; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: Lung Function at End of Treatment - Actual outcome for Adults and young people overall: FEV1 L at 12 months; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 6: Symptom free days at End of Treatment - Actual outcome for Adults and young people overall: % symptom free days in previous 2 weeks at 12 months; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Rescue medication at End of Treatment; Time of school/work at End of Treatment

Table 118: MEHUYS 2008[1116]

Study	**Mehuys 2008[1116]**
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=201)
Countries and setting	Conducted in Belgium; Setting: Pharmacy, multicentre
Line of therapy	Mixed line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Asthma patients
Stratum	Adults and young people overall: Asthma patients treated for asthma for ≥12 months (not including fully controlled or severely uncontrolled)
Subgroup analysis within study	Not applicable: na
Inclusion criteria	Aged 18-50 years; treated for asthma for ≥12 months; using controller medication; regular visitor to the pharmacy.
Exclusion criteria	Smoking history of >10 pack-years; suffering from another severe disease and ACT at screening of <15 (indicating seriously uncontrolled asthma) or equalling 25 (complete asthma control).
Recruitment/selection of patients	Consecutive recruitment in 66 pharmacies from Jan 2006 - April 2006.
Age, gender and ethnicity	Age - Range: 18-50. Gender (M:F): 94/107. Ethnicity:
Further population details	1. Education level: Not applicable / Not stated / Unclear 2. Language: Non English speaking (Non English speaking but Dutch version of ACT used).
Extra comments	Baseline data: Mean (range) age: Monitoring: 35.2 (19-51); Usual care: 36.3 (17-51). ACT mean (range): Monitoring: 19.7 (11-25); Usual care: 19.3 (10-25). ICS %: Monitoring: 25%; Usual care: 23.1%; LABA/ICS %: Monitoring: 64.5%; Usual care: 70.8%.
Indirectness of population	No indirectness
Interventions	(n=107) Intervention 1: Monitoring asthma control + treatment - Monitoring control questionnaires + treatment. Pharmacist intervention including initial education on inhaler technique, asthma, medication. Pharmacist advice at 1 month and 3 months based on ACT score of the patient (direct physician feedback). -ACT <15 (uncontrolled asthma): immediate referral to GP or specialist-ACT 15-19 (insufficiently controlled asthma): review inhaler technique and check controller adherence-ACT >19 (well-controlled): no advice, inform patient asthma is well-controlled. Duration 6 months. Concurrent medication/care: Education session from pharmacist at the start of the intervention in the intervention group Further details: 1. Additional education training : Not applicable / Not stated / Unclear 2. Duration of study: >= 6 months (n=94) Intervention 2: Usual care. Usual pharmacist care. Duration 6 months. Concurrent medication/care: No education at start of study as in intervention group.

	Further details: 1. Additional education training : Not applicable / Not stated / Unclear 2. Duration of study: >= 6 months
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ONGOING MANAGEMENT BASED ON ACT SCORE versus USUAL PHARMACIST CARE

Protocol outcome 1: Quality of life at End of treatment
- Actual outcome for Adults and young people overall: AQLQ at 6 months; Group 1: mean 6 (SD 0.7); n=80, Group 2: mean 5.8 (SD 0.9); n=70; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Exacerbation (need for OCS) at End of treatment
- Actual outcome for Adults and young people overall: Exacerbation (ER visit, hospitalisation or course of OCS) at 6 months; Group 1: 10/80, Group 2: 8/70; Risk of bias: Very high; Indirectness of outcome: Serious indirectness

Protocol outcome 3: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment
- Actual outcome for Adults and young people overall: ER visit or hospitalisation at 6 months; Group 1: 1/80, Group 2: 5/70; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 4: Asthma control questionnaires at End of Treatment
- Actual outcome for Adults and young people overall: ACT final values at 3 months; Group 1: mean 20.3 (SD 3.2); n=99, Group 2: mean 20 (SD 3.8); n=84; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adults and young people overall: ACT final values at 6 months; Group 1: mean 20.2 (SD 3.5); n=80, Group 2: mean 19.7 (SD 4.8); n=70; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adults and young people overall: ACT, no. of patients controlled (score 20-25) at 3 months; Group 1: 61/99, Group 2: 52/84; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adults and young people overall: ACT, no. of patients controlled (score 20-25) at 6 months; Group 1: 54/80, Group 2: 42/70; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults and young people overall: ACT, no. of patients partially controlled (score 15-19) at 3 months; Group 1: 32/99, Group 2: 23/84; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adults and young people overall: ACT, no. of patients partially controlled (score 15-19) at 6 months; Group 1: 19/80, Group 2: 17/70; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adults and young people overall: ACT, no. of patients uncontrolled (score <15) at 3 months; Group 1: 5/99, Group 2: 9/84; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adults and young people overall: ACT, no. of patients uncontrolled (score <15) at 6 months; Group 1: 7/80, Group 2: 11/70; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 5: Rescue medication at End of Treatment - Actual outcome for Adults and young people overall: puffs/day final values at 3 months; Group 1: mean 0.68 puffs/day (SD 1.16); n=99, Group 2: mean 1.3 puffs/day (SD 2.55); n=84; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people overall: puffs/day final values at 6 months; Group 1: mean 0.67 puffs/day (SD 1.33); n=80, Group 2: mean 0.9 puffs/day (SD 1.36); n=70; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Lung Function at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Table 119: RIKKERSMUTSAERTS 2012[1449]

Study	**SMASHING trial: Rikkers-mutsaerts 2012[1449]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in Netherlands; Setting: Primary and Secondary care
Line of therapy	Mixed line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Doctor Dx of mild to severe persistant asthma; not well controlled asthma as assessed by ACQ>0.75 and/or ATAQ <1.0
Stratum	Children 5 -<16 with uncontrolled asthma: Children 12-18 years, asthma not well controlled asthma as assessed by ACQ>0.75 and/or ATAQ <1.0
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 12-18 years; prescription of ICS for more than 3 months in the previous year; access to the internet; Dutch language
Exclusion criteria	Receiving maintenance OCS treatment; relevant co-morbidity.
Age, gender and ethnicity	Age - Range: 12-18 years. Gender (M:F): 45/45. Ethnicity:
Further population details	1. Education level: Not applicable / Not stated / Unclear 2. Language: Non English speaking (Dutch speaking).
Extra comments	Baseline data: Age mean (range) Monitoring: 13.4 (12-17), UC: 13.8 (12-17); FEV1%pred Monitoring: 88 (49-151), UC: 92 (49-164); AQLQ Monitoring: 5.6 (3.12-6.97), UC: 5.68 (2.87-7.0); ACQ Monitoring: 1.29 (0.22-3.0), UC: 1.19 (0-3.43); %

	ICS Monitoring: 100%, UC: 100%; % ICS/LABA Monitoring: 60.5%, UC: 65%.
Indirectness of population	Serious indirectness: Age group indirect to protocol (12-18 years); not well controlled asthma includes partially controlled and uncontrolled (not uncontrolled alone)
Interventions	(n=46) Intervention 1: Monitoring asthma control + treatment - Monitoring control questionnaires + treatment. Weekly asthma control monitoring (according to ACQ score) and treatment advice. Monitoring through website, use of internet based treatment plan, online education, web communications with an asthma nurse. Weekly completion of electronic ACQ and instant feedback of asthma control along with advice on how to adjust treatment according to predefined algorithm and treatment plan (treatment steps according to GINA). Patients attended their own physician, as they would normally do, every 3–6 months and extra when needed if their asthma was deteriorating).. Duration 12 months. Concurrent medication/care: Intervention group only: online education, face-to-face group education (two 60 min sessions) and web communications with an asthma nurse.Both groups received prior basic education about asthma, medications and inhaler technique. All trained to measure FEV1 daily and report highest value of 3 measurements before medications. Reported ACQ weekly. No feedback provided on ACQ or lung function. Further details: 1. Additional education training : Additional education in both groups 2. Duration of study: >= 6 months (n=44) Intervention 2: Usual care. Usual care. Adolescents in the usual care group received care by their physician according to the Dutch guidelines on asthma management in children in general practice and in hospitals. Commonly, they visited their general practitioner or paediatrician every 3 months or twice per year once control of asthma had been achieved.. Duration 12 months. Concurrent medication/care: Both groups received prior basic education about asthma, medications and inhaler technique. All trained to measure FEV1 daily and report highest value of 3 measurements before medications. Reported ACQ weekly. No feedback provided on ACQ or lung function. Further details: 1. Additional education training : Additional education in both groups 2. Duration of study: >= 6 months
Funding	Academic or government funding (Netherlands Asthma Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ONGOING MANAGEMENT BASED ON ACQ SOCRE versus USUAL CARE + TREATMENT

Protocol outcome 1: Quality of life at End of treatment
- Actual outcome for Children 5 -<16 with uncontrolled asthma: PAQLQ at 3 months; MD 0.4 (95%CI 0.17 to 0.62) (P<0.05) PAQLQ 1-7 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Children 5 -<16 with uncontrolled asthma: PAQLQ at 12 months; MD -0.05 (95%CI -0.5 to 0.41) (P=0.85) PAQLQ 1-7 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Exacerbation (need for OCS) at End of treatment

- Actual outcome for Children 5 -<16 with uncontrolled asthma: Exacerbation requiring OCS for 3 days or more at 12 months; Group 1: 6/35, Group 2: 6/40; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Asthma control questionnaires at End of Treatment - Actual outcome for Children 5 -<16 with uncontrolled asthma: ACQ at 3 months; MD -0.32 (95%CI -0.56 to -0.079) (P<0.01) ACQ 0-6 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children 5 -<16 with uncontrolled asthma: ACQ at 12 months; MD -0.05 (95%CI -0.35 to 0.25) (P=0.75) ACQ 0-6 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 4: Dose of regular asthma treatment (SABA, ICS) at End of Treatment - Actual outcome for Children 5 -<16 with uncontrolled asthma: Mean daily ICS use µg at 3 months; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children 5 -<16 with uncontrolled asthma: Mean daily ICS use µg at 12 months; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 5: Lung Function at End of Treatment - Actual outcome for Children 5 -<16 with uncontrolled asthma: FEV1 L at 3 months; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children 5 -<16 with uncontrolled asthma: FEV1 L at 12 months; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 6: Symptom free days at End of Treatment - Actual outcome for Children 5 -<16 with uncontrolled asthma: Proportion of symptom free days in the previous 2 weeks at 3 months; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children 5 -<16 with uncontrolled asthma: Proportion of symptom free days in the previous 2 weeks at 12 months; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Rescue medication at End of Treatment; Time of school/work at End of Treatment

G.16 Lung function tests to monitor asthma control

Table 120: Adams 2001[15]

Study	**Adams 2001[15]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=N=172 (no. randomised to each group not reported and also high attrition from ACA numbers - high ROB))

Countries and setting	Conducted in Australia; Setting: Secondary care (university public teaching hospital)
Line of therapy	Mixed line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Physician's diagnosis of asthma defined by American Thoracic Society
Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 17 to 70 years; physician's diagnosis of asthma defined by American Thoracic Society; demonstrated ability to use PFM; telephone access at home; could read and sign consent form in English
Exclusion criteria	Previous life-threatening attack of asthma, current or previous written asthma action plan based on symptoms or PEF; pregnancy; poor perception of bronchoconstriction during histamine inhalation test; baseline FEV1 <1.5L preventing histamine inhalation test
Recruitment/selection of patients	Recruited from inpatient and outpatient clinics
Age, gender and ethnicity	Age - Range of means: PFM group 37.3, symptoms group 35.5 years. Gender (M:F): 52:82. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	(n=73) Intervention 1: Monitoring lung function + treatment - Monitoring PEF + treatment. Self-management action plan activated by decrease in PEF explained by specialist pulmonologist; reinforced monthly by study coordinator. Duration 12 months. Concurrent medication/care: Started or continued on appropriate dose of inhaled corticosteroids; instructed to use bronchodilator as required Further details: 1. Additional education training : Additional education in both groups (n=61) Intervention 2: No lung function monitoring + treatment - Monitoring symptoms + treatment. Self-management action plan activated by increase in symptoms explained by specialist pulmonologist; reinforced monthly by study coordinator. Duration 12 months. Concurrent medication/care: Started or continued on appropriate dose of inhaled corticosteroids; instructed to use bronchodilator as required Further details: 1. Additional education training : Additional education in both groups
Funding	Academic or government funding (University of Adelaide, The Queen Elizabeth Hospital Research Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING PEF + TREATMENT versus MONITORING SYMPTOMS + TREATMENT

Protocol outcome 1: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment - Actual outcome for Adults and young people (16 years and over): Hospitalisation days at 12 months; Group 1: mean 0.07 days (SD -0.3); n=48, Group 2: mean 0.1 days (SD 0.5); n=40; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people (16 years and over): ED visits at 12 months; Group 1: mean 0.11 (SD 0.4); n=48, Group 2: mean 0.15 (SD 0.4); n=40; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Asthma control questionnaires at End of Treatment - Actual outcome for Adults and young people (16 years and over): Severity self-rating at 12 months; Group 1: mean 3.46 None (SD 3.3); n=48, Group 2: mean 3.48 None (SD 2.5); n=40; Self-rating asthma severity 0-10 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Lung Function at End of Treatment - Actual outcome for Adults and young people (16 years and over): Pre-bronchidilator FEV1 at 12 months; Group 1: mean 2.45 L (SD 0.82); n=48, Group 2: mean 2.71 L (SD 0.86); n=40; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 4: Time of school/work at End of Treatment - Actual outcome for Adults and young people (16 years and over): Days off work at 12 months; Group 1: mean 5 days (SD 11); n=48, Group 2: mean 2.3 days (SD 4); n=40; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; Exacerbation (need for OCS) at End of treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Symptom free days at End of Treatment

Table 121: Buist 2006[243]

Study	**Buist 2006[243]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=296)
Countries and setting	Conducted in USA; Setting: Community
Line of therapy	Not applicable
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Physician-diagnosed asthma and had medication use suggestive of moderate-to-severe asthma; bronchodilator reversibility (> 8% of baseline FEV1)

Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 50 to 92 yr, recruited from a large managed-care organization; physician-diagnosed asthma and medication use suggestive of moderate-to-severe asthma; none was using a peak flow meter; screening criteria included bronchodilator reversibility (>8% of baseline FEV1) and demonstrated ability to keep a daily symptom diary.
Exclusion criteria	None apart from above
Recruitment/selection of patients	Screening criteria included bronchodilator reversibility (> 8% of baseline FEV1) and demonstrated ability to keep a daily symptom diary.
Age, gender and ethnicity	Age - Mean (SD): 66 (9.4) years. Gender (M:F): 142:154. Ethnicity: 94% were white, not of Hispanic origin; others not stated
Further population details	
Indirectness of population	No indirectness
Interventions	(n=149) Intervention 1: Monitoring lung function + treatment - Monitoring PEF + treatment. Peak flow rate (twice daily or “as needed”) for asthma monitoring; four 90-min small-group classes. Development of a personalised action plan and review of the subjects’ asthma diaries; instructed in proper use of metered dose inhalers (MDIs). Interventionists also met with participants semiannually to review MDI and peak flow technique, review daily diaries, and discuss participants’ action plans. In between these meetings, they phoned participants quarterly to review diaries and answer questions . Duration 2 years. Concurrent medication/care: Not stated Further details: 1. Additional education training : (n=147) Intervention 2: No lung function monitoring + treatment - Monitoring symptoms + treatment. Symptoms for asthma monitoring; four 90-min small-group classes. Development of a personalised action plan and review of the subjects’ asthma diaries; instructed in proper use of metered dose inhalers (MDIs). Interventionists also met with participants semiannually to review MDI and peak flow technique, review daily diaries, and discuss participants’ action plans. In between these meetings, they phoned participants quarterly to review diaries and answer questions . Duration 2 years. Concurrent medication/care: Not stated Further details: 1. Additional education training :
Funding	Academic or government funding (National Heart, Lung, and Blood Institute)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING PEF + TREATMENT versus MONITORING SYMPTOMS + TREATMENT	

Protocol outcome 1: Quality of life at End of treatment - Actual outcome for Adults and young people (16 years and over): AQLQ increase >0.5 points at 2 years; Group 1: 52/134, Group 2: 50/128; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people (16 years and over): AQLQ decrease >0.5 points at 2 years; Group 1: 16/134, Group 2: 11/128; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment - Actual outcome for Adults and young people (16 years and over): Total asthma-related health care utilisation at 2 years; Group 1: mean 1.39 Events per person-year of follow-up (SD 1.98); n=148, Group 2: mean 1.5 Events per person-year of follow-up (SD 2.23); n=146; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Exacerbation (need for OCS) at End of treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Lung Function at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Table 122: Charlton 1990[302]

Study	**Charlton 1990[302]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=115 Patients (46 children and 69 adults))
Countries and setting	Conducted in United Kingdom; Setting: General practice
Line of therapy	Not applicable
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients on the repeat prescribing register who were receiving prophylactic treatment for asthma.
Stratum	Adults and young people (16 years and over)

Subgroup analysis within study	Not applicable
Inclusion criteria	Patients on the repeat prescribing register who were receiving prophylactic treatment for asthma.
Exclusion criteria	Not stated
Recruitment/selection of patients	Patients on the repeat prescribing register who were receiving prophylactic treatment for asthma.
Age, gender and ethnicity	Age - --: Not stated. Gender (M:F): Not stated. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	(n=51) Intervention 1: Monitoring lung function + treatment - Monitoring PEF + treatment. Peak flow self-management plan. The first interview usually took 45 minutes. One week later the patients were reviewed by the nurse for a further 15 minutes, when spirometry was again performed and inhaler technique checked. Progress with self monitoring and self management were checked and treatment altered, if necessary, after discussion with the patient's general practitioner. Topics such as smoking, holidays, provoking factors, and emergency treatments were discussed in the course of the follow up visits. All the patients were reviewed every eight weeks by the nurse or more often if she considered it necessary.. Duration 12 months. Concurrent medication/care: Not stated Further details: 1. Additional education training : Additional education in both groups (n=64) Intervention 2: No lung function monitoring + treatment - Monitoring symptoms + treatment. Symptoms self-management plan. The first interview usually took 45 minutes. One week later the patients were reviewed by the nurse for a further 15 minutes, when spirometry was again performed and inhaler technique checked. Progress with self monitoring and self management were checked and treatment altered, if necessary, after discussion with the patient's general practitioner. Topics such as smoking, holidays, provoking factors, and emergency treatments were discussed in the course of the follow up visits. All the patients were reviewed every eight weeks by the nurse or more often if she considered it necessary.. Duration 12 months. Concurrent medication/care: Not stated Further details: 1. Additional education training : Additional education in both groups
Funding	Academic or government funding (Clare Wand fund, the Scientific Foundation of the Royal College of General

	Practitioners, and Vitalograph)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING PEF + TREATMENT versus MONITORING SYMPTOMS + TREATMENT Protocol outcome 1: Exacerbation (need for OCS) at End of treatment - Actual outcome for Adults and young people (16 years and over): Receiving oral steroids at 12 months; Group 1: 14/27, Group 2: 7/33; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children 5 -<16 : Receiving oral steroids at 12 months; Group 1: 7/19, Group 2: 0/27; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Rescue medication at End of Treatment - Actual outcome for Adults and young people (16 years and over): Requiring nebulised salbutamol at 12 months; Group 1: 3/28, Group 2: 2/37; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children 5 -<16 : Requiring nebulised salbutamol at 12 months; Group 1: 2/17, Group 2: 0/27; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Lung Function at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Table 123: Cote 1997[364]

Study	**Cote 1997[364]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=188)
Countries and setting	Conducted in Canada; Setting: Three tertiary care hospitals
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: The diagnosis had to be confirmed by either a documented reversibility greater than 15% in FEV1 or a methacholine PC20<8mg/ml

Stratum	Adults and young people (16 years and over): Aged 16 years or older
Subgroup analysis within study	Not applicable
Inclusion criteria	Presence of moderate to severe asthma; aged 16 years or older; the need to take daily anti-inflammatory agents (ICS, cromoglycate or nedocromil).
Exclusion criteria	Current or ex-smokers 40 years of age or older in whom the best FEV1 after salbutamol was <80% predicted; patients with significant concurrent diseases; tose requiring >7.5mg/day of prednisone to control asthma symptoms, those having taken part in an asthma educational program. Subjects in whom regular OCS were needed to obtain good asthma control during the run-in period were excluded.
Recruitment/selection of patients	At time of hospitalisation or visit to the clinic between April and December 1993
Age, gender and ethnicity	Age - Range: ≥16 years. Gender (M:F): 37/58. Ethnicity:
Further population details	
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Monitoring lung function + treatment - Monitoring PEF + treatment. Self-management based on twice daily PEF. - Step 1: green zone, morning PEF ≥85% best, continue maintenance treatment- Step 2: yellow zone, for past 24 hours PEF 60-85% best, increase BDP to 4 puffs twice daily (2000mcg/day) until PEF % best returns, or if there is no increase in PEF within 48 hours proceed to step 3.- Step 3: red zone, for past 12 hours PEF <60% best, inform physician and start OCS- Step 4: red extra zone, PEF <50% best, visit physician or ER.. Duration 12 months. Concurrent medication/care: 2-6 week run-in period when medication adjusted according to the International Consensus on asthma therapy. In patients receiving budesonide, this was replaced by an equivalent dose of inhaled beclomethasone dipropionate (BDP). In patients considered unstable during run-in period (nighttime symptoms, four or more puffs/day of inhaler beta-agonist, PEFv>15%, post-BD FEV1<85%, mean PEF <85%) the dose of BDP could be doubled or theophyllines added. Subjects in whom regular OCS were needed to obtain good asthma control were excluded. Both groups received counselling with an educator during a 1 hour session. Further details: 1. Additional education training : Additional education in both groups (n=45) Intervention 2: No lung function monitoring + treatment - Monitoring symptoms + treatment. Self-management based on symptoms. - Step 1: green zone, not awakened at night, using usual SABA and able to perform usual activities, continue maintenance treatment- Step 2: yellow zone, for previous 24 hours using twice as much SABA, awakened at night and unusual breathlessness with exercise, increase BDP to 4 puffs twice daily (2000mcg/day) until PEF % best returns, or if there is no increase in PEF within 48 hours proceed to step 3.- Step 3: red zone, for past 24 hours SABA relieving symptoms for <4 hours or more than 10puffs/day, inform physician and start OCS- Step 4: red extra zone, SABA relieving symptoms for <2 hours and difficulty talking, inform physician and visit ER.. Duration 12 months. Concurrent

	medication/care: 2-6 week run-in period when medication adjusted according to the International Consensus on asthma therapy. In patients receiving budesonide, this was replaced by an equivalent dose of inhaled beclomethasone dipropionate (BDP). In patients considered unstable during run-in period (nighttime symptoms, four or more puffs/day of inhaler beta-agonist, PEFv>15%, post-BD FEV1<85%, mean PEF <85%) the dose of BDP could be doubled or theophyllines added. Subjects in whom regular OCS were needed to obtain good asthma control were excluded. Both groups received counselling with an educator during a 1 hour session. Further details: 1. Additional education training : Additional education in both groups
Funding	Study funded by industry (Supported by a grant from Glaxo Canada, Mississauga (Ontario))
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING PEF + TREATMENT versus MONITORING SYMPTOMS + TREATMENT Protocol outcome 1: Exacerbation (need for OCS) at End of treatment - Actual outcome for Adults and young people (16 years and over): OCS courses at 12 months; Group 1: mean 0.7 number of events (SD 1.4); n=50, Group 2: mean 0.9 number of events (SD 1.3); n=45; Risk of bias: Very high; Indirectness of outcome: Serious indirectness Protocol outcome 2: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment - Actual outcome for Adults and young people (16 years and over): Hospitalisation at 12 months; Group 1: mean 0.04 number of events (SD 0.28); n=50, Group 2: mean 0.09 number of events (SD 0.27); n=45; Risk of bias: Very high; Indirectness of outcome: Serious indirectness - Actual outcome for Adults and young people (16 years and over): ER visits at 12 months; Group 1: mean 0.7 number of events (SD 1.4); n=50, Group 2: mean 0.7 number of events (SD 1.3); n=50; Risk of bias: Very high; Indirectness of outcome: Serious indirectness Protocol outcome 3: Time of school/work at End of Treatment - Actual outcome for Adults and young people (16 years and over): Mean number of days lost from school or work at 12 months; Group 1: mean 2.2 number of days lost (SD 12.7); n=50, Group 2: mean 2.9 number of days lost (SD 12.7); n=45; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Lung Function at End of Treatment; Symptom free days at End of Treatment

Table 124: Cowie 1997[369]

Study	**Cowie 1997[369]**
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=150)
Countries and setting	Conducted in Canada; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Adult and adolescent patients who had received urgent treatment for their asthma in the preceding 12 months and used asthma medication
Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult and adolescent patients who had received urgent treatment for their asthma in the preceding 12 months and used asthma medication
Exclusion criteria	Not stated
Recruitment/selection of patients	Subjects were recruited by contacting those who had been treated for an exacerbation of asthma in an emergency department in one of the teaching hospitals in the city of Calgary. Subjects were also recruited from those attending a university asthma clinic when they gave a history of having received urgent treatment for their asthma in the previous 12 months.
Age, gender and ethnicity	Age - Range of means: 36.4 to 39.1 years. Gender (M:F): 56:83. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	(n=48) Intervention 1: Monitoring lung function + treatment - Monitoring PEF + treatment. Patients were given a peak flowmeter and brief instructions in its use and in recording the data. Their action plan included peak flow measurements that were estimated from their measured and predicted peak expiratory flows. Peak flow readings at or below which each step should be initiated were written into each subject's action plan. Doubling of their inhaled corticosteroid was recommended when the peak expiratory flow was <70% of their estimated best reading or when the diurnal variation was >20%. Initiation of the third step (prednisone) was advised at <50%, and the fourth step (urgent treatment in an emergency department) at <30% of their estimated best peak expiratory flow.. Duration 6 months. Concurrent medication/care: Not stated Further details: 1. Additional education training : (n=50) Intervention 2: No lung function monitoring + treatment - Monitoring symptoms + treatment. The instructions for the symptom-based plan listed common symptoms of asthma, including waking at night or a persistent cough and

	symptoms of a common cold as indications for doubling their inhaled corticosteroid. The third step required the introduction of prednisone if their relief following the use of a bronchodilator lasted <2 h or if they became short of breath doing their normal daily activities. The fourth step required them to seek urgent treatment if their bronchodilator provided relief for <30 min or if their breathing made it difficult for them to speak.. Duration 6 months. Concurrent medication/care: Not stated Further details: 1. Additional education training :
Funding	Academic or government funding (Foothills Hospital Calgary)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING PEF + TREATMENT versus MONITORING SYMPTOMS + TREATMENT Protocol outcome 1: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment - Actual outcome for Adults and young people (16 years and over): Visits for urgent treatment of asthma at 6 months; Group 1: 5/46, Group 2: 14/45; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people (16 years and over): Hospital admissions at 6 months; Group 1: 2/46, Group 2: 2/45; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; Exacerbation (need for OCS) at End of treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Lung Function at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Table 125: Kaya 2009[827]

Study	**Kaya 2009[827]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=63)
Countries and setting	Conducted in Turkey; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients with persistent asthma; had been receiving care for at least 1 year in specific asthma clinic; classified by GINA guidelines on illness severity

Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with persistent asthma; had been receiving care for at least 1 year in specific asthma clinic; classified by GINA guidelines on illness severity
Exclusion criteria	Significant co-morbid conditions; illiteracy; hearing and visual defects; mental retardation; psychotic disorders
Recruitment/selection of patients	Specific asthma clinic
Age, gender and ethnicity	Age - Mean (SD): 43 (10.48) years. Gender (M:F): 13:50. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	(n=31) Intervention 1: Monitoring lung function + treatment - Monitoring PEF + treatment. PEF-based self-management. Duration 12 months. Concurrent medication/care: Standard education programme on asthma self-management prepared according to GINA recommendations given to patients with booklet for keeping daily reords Further details: 1. Additional education training : Additional education in both groups (n=32) Intervention 2: No lung function monitoring + treatment - Monitoring symptoms + treatment. Symptom-based self-monitoring. Duration 12 months. Concurrent medication/care: Standard education programme on asthma self-management prepared according to GINA recommendations given to patients with booklet for keeping daily reords Further details: 1. Additional education training : Additional education in both groups
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING PEF + TREATMENT versus MONITORING SYMPTOMS + TREATMENT

Protocol outcome 1: Quality of life at End of treatment
- Actual outcome for Adults and young people (16 years and over): SF-36 physical score at 3 months; Group 1: mean 58.81 None (SD 21.98); n=31, Group 2: mean 65.3 None (SD 21.31); n=32; SF-36 Physical 0-100 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adults and young people (16 years and over): SF-36 mental score at 3 months; Group 1: mean 62.39 None (SD 19.1); n=31, Group 2: mean 74.17 None (SD 15.51); n=32; SF-36 Mental 0-100 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung Function at End of Treatment
- Actual outcome for Adults and young people (16 years and over): FEV1 (%) at 6 months; Group 1: mean 87.74 % (SD 19.02); n=31, Group 2: mean 87.35 % (SD 21.25); n=32; Risk of bias: Very high; Indirectness of outcome: No indirectness

- Actual outcome for Adults and young people (16 years and over): PEF (% personal best) at 6 months; Group 1: mean 84.93 % (SD 14.32); n=31, Group 2: mean 79.62 % (SD 14.92); n=32; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Exacerbation (need for OCS) at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Table 126: Letz 2004[985]

Study	**Letz 2004[985]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in USA; Setting: Allergy, asthma and immunology clinic
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 3 month
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosed with mild to severe persistent asthma (symptoms at least 2 times per week, FEV1<80% and FEV1 or PEF variability 12% or greater). Diagnosis made on the basis of history, examination and pre/post-BD lung function testing.
Stratum	Children 5 -<16 : 6-12 years
Subgroup analysis within study	Not applicable
Inclusion criteria	6-12 years, diagnosed with mild to severe persistent asthma (symptoms at least 2 times per week, FEV1<80% and FEV1 or PEF variability 12% or greater), new diagnosis and initiation of daily ICS.
Exclusion criteria	nr
Recruitment/selection of patients	Consecutive recruitment at 2 week follow up after diagnosis and initiation of ICS.
Age, gender and ethnicity	Age - Range of means: 8.9-9.4. Gender (M:F): 32/18. Ethnicity: Caucasian
Further population details	
Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: Monitoring lung function + treatment - Monitoring PEF + treatment. Action plan based on

	patient's measured and predicted PEF values. Yellow zone recommended when PEF 60-80%, red zone when PEF <60%. Best of 3 consecutive PEF readings recorded daily. Baseline therapy with ICS (green zone), step-up of ICS and beta-agonists used every 4 hours (yellow zone), call office or present to emergency room (red zone). . Duration 3 months. Concurrent medication/care: All provided with asthma education session from a nurse including use of the action plan. Further details: 1. Additional education training : Additional education in both groups (n=25) Intervention 2: No lung function monitoring + treatment - Monitoring symptoms + treatment. Action plan based on symptoms only. Common symptoms including persistent cough, symptoms of common cold, dyspnoea as indications for initiating yellow zone. Red zone if relief following a BD lasted less than 2 hours. Baseline therapy with ICS (green zone), step-up of ICS and beta-agonists used every 4 hours (yellow zone), call office or present to emergency room (red zone).. Duration 3 months. Concurrent medication/care: All provided with asthma education session from a nurse including use of the action plan. Further details: 1. Additional education training : Additional education in both groups
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING PEF + TREATMENT versus MONITORING SYMPTOMS + TREATMENT Protocol outcome 1: Exacerbation (need for OCS) at End of treatment - Actual outcome for Children 5 -<16 : Required a course of OCS at 3 month; Group 1: 1/12, Group 2: 1/12; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Lung Function at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Table 127: Lopez-vina 2000[1027]

Study	**Lopez-vina 2000[1027]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=150)
Countries and setting	Conducted in Spain

Line of therapy	Mixed line
Duration of study	Intervention + follow up: 12 month
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Satisfied the ATS definition of asthma, with symptoms of episodic wheezing, cough and shortness of breath responding to bronchodilators, and reversible airflow obstruction documented on at least one previous pulmonary function study (>20% increase in FEV1 or PEF following salbutamol 0.2mg). In patients with normal spirometry and lac of functional assessment of asthma previously, a methacholine test was performed.
Stratum	Adults and young people (16 years and over): 17-65 years of age
Subgroup analysis within study	Not applicable
Inclusion criteria	17-65 years of age; required treatment in an ED of acute-care hospitals over an 18-month period because of an episode of acute asthma exacerbation; symptomatic disease during the previous year; satisfied the ATS definition of asthma with BDR or BHR.
Exclusion criteria	Concurrent chronic diseases (COPD, emphysema, cystic fibrosis, severe rheumatoid arthritis, neoplasia etc)
Recruitment/selection of patients	Consecutive patients who required treatment in an ED over an 18-month period
Age, gender and ethnicity	Age - Range: 17-65. Gender (M:F): 49/51. Ethnicity:
Further population details	
Indirectness of population	No indirectness
Interventions	(n=75) Intervention 1: Monitoring lung function + treatment - Monitoring PEF and symptoms + treatment. Self-management plan with a card of colour codes based on symptoms, medication and PEF. Physician assessment at 15 days, 1 month and then every 3 months at which treatment adjusted according to symptoms, spirometric data and variability in PEF (less than 10% variability considered irrelevant). Duration 12 months. Concurrent medication/care: Medical regimes tailored to each patient and included the administration of beta-agonists when needed in mild asthma; inhaled salbutamol 0.2mg or terbutaline 0.5mg and budesonide 400mcg every 12 hours in moderate to severe asthma with FEV1>80%; and inhaled salbutamol 0.2mg or terbutaline 0.5mg and budesonide 800mcg every 8 hours or when needed and prednisone 40mg/day for 14 days in moderate to severe asthma with FEV1<80%. Patients in both groups received asthma education. Further details: 1. Additional education training : Additional education in both groups (n=75) Intervention 2: No lung function monitoring + treatment - Monitoring symptoms + treatment. Self-management plan based on symptoms only. Physician assessment at 15 days, 1 month and then every 3 months at which treatment adjusted according to symptoms and spirometric data only.. Duration 12 months. Concurrent medication/care: Medical regimes tailored to each patient and included the administration of beta-agonists when needed in mild asthma; inhaled

	salbutamol 0.2mg or terbutaline 0.5mg and budesonide 400mcg every 12 hours in moderate to severe asthma with FEV1>80%; and inhaled salbutamol 0.2mg or terbutaline 0.5mg and budesonide 800mcg every 8 hours or when needed and prednisone 40mg/day for 14 days in moderate to severe asthma with FEV1<80%. Patients in both groups received asthma education. Further details: 1. Additional education training : Additional education in both groups
Funding	Academic or government funding (Supported in part by grant FISS 92/372)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING PEF, MEDICATION AND SYMPTOMS + TREATMENT versus MONITORING SYMPTOMS + TREATMENT Protocol outcome 1: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment - Actual outcome for Adults and young people (16 years and over): Number of patients with visits to an emergency ward at 12 months; Group 1: 3/56, Group 2: 0/44; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people (16 years and over): Number of patients with a hospital admission at 12 months; Group 1: 2/56, Group 2: 0/44; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Lung Function at End of Treatment - Actual outcome for Adults and young people (16 years and over): FEV1% predicted at 12 months; Group 1: mean 80.9 % (SD 2.3); n=56, Group 2: mean 80.8 % (SD 2.8); n=44; FEV1 %pred 0-100 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Time of school/work at End of Treatment - Actual outcome for Adults and young people (16 years and over): Number of patients with absenteeism school/work at 12 months; Group 1: 2/56, Group 2: 0/44; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; Exacerbation (need for OCS) at End of treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Symptom free days at End of Treatment

Table 128: Turner 1998[1783]

Study	**Turner 1998[1783]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=117)

Countries and setting	Conducted in Canada; Setting: Primary care
Line of therapy	Not applicable
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: PC20 methacholine < 8 mg/ml
Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Between 18 and 55 yr of age with moderate to moderately severe asthma. The authors defined asthma severity by including only patients with a baseline PC20 methacholine < 8 mg/ml and a daily requirement for inhaled corticosteroids to manage their asthma symptoms. Patients were either newly prescribed inhaled corticosteroids independently by their family physician or were currently using inhaled corticosteroids.
Exclusion criteria	Exclusion criteria included significant comorbid conditions that would impact on QOL measurements, current use of a PFM, inability to use a PFM, and inability to communicate in English.
Recruitment/selection of patients	Potential study patients were identified from the clinic computer database, and the clinic physicians were encouraged to refer patients meeting study criteria. The authors displayed a poster board and flyer advertisements in the clinic to encourage volunteers. All patients had written permission from their physician to participate.
Age, gender and ethnicity	Age - Mean (SD): PEF group: 34.1 (10.5); symptoms group: 34.1 (9.4) years. Gender (M:F): 43:49. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	(n=53) Intervention 1: Monitoring lung function + treatment - Monitoring PEF + treatment. The asthma nurse reviewed patients monthly for 6 mo after the initial visit (seven total visits). The self-management plans and use of a PFM were reviewed in detail after randomization. Monthly visits documented morbidity outcomes, reinforced and evaluated use of the self-management plan, and provided ongoing education. Duration 6 months. Concurrent medication/care: Not stated Further details: 1. Additional education training : (n=64) Intervention 2: No lung function monitoring + treatment - Monitoring symptoms + treatment. The asthma nurse reviewed patients monthly for 6 mo after the initial visit (seven total visits). The self-management plans were reviewed in detail after randomization. Monthly visits documented morbidity outcomes, reinforced and evaluated use of the self-management plan, and provided ongoing education. Duration 6 months. Concurrent medication/care: Not stated Further details: 1. Additional education training :

Funding	Study funded by industry (Glaxo Wellcome Canada Inc.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING PEF + TREATMENT versus MONITORING SYMPTOMS + TREATMENT Protocol outcome 1: Quality of life at End of treatment - Actual outcome for Adults and young people (16 years and over): Asthma Quality of Life Questionnaire at 6 months; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Exacerbation (need for OCS) at End of treatment - Actual outcome for Adults and young people (16 years and over): Prednisone treatments at 6 months; Group 1: 3/44, Group 2: 6/48; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment - Actual outcome for Adults and young people (16 years and over): Unscheduled doctor visits at 6 months; Group 1: 17/44, Group 2: 12/48; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people (16 years and over): Hospitalisation at 6 months; Group 1: 0/44, Group 2: 1/48; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people (16 years and over): ED visits at 6 months; Group 1: 6/44, Group 2: 2/48; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 4: Lung Function at End of Treatment - Actual outcome for Adults and young people (16 years and over): FEV1 % pred at 6 months; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people (16 years and over): PEF at 6 months; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: Time of school/work at End of Treatment - Actual outcome for Adults and young people (16 years and over): Time off school/work at 6 months; Group 1: 9/44, Group 2: 8/48; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Symptom free days at End of Treatment

Table 129: Wensley 2004[1885]

Study	**Wensley 2004[1885]**
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in United Kingdom; Setting: Recruitment in primary care and secondary care.
Line of therapy	Not applicable
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Physician-diagnosed asthma and at least step 2 of the British Thoracic Society Guidelines for Asthma Management (regular inhaled corticosteroid therapy)
Stratum	Children 5 -<16
Subgroup analysis within study	Not applicable
Inclusion criteria	Inclusion criteria were (1) age 7–14 years, (2) physician-diagnosed asthma, (3) at least step 2 of the British Thoracic Society Guidelines for Asthma Management (regular inhaled corticosteroid therapy), (4) stable treatment for 1 month, (5) no other respiratory problem, (6) competent at spirometry, and (7) a successful 4-week run-in period.
Exclusion criteria	None stated
Recruitment/selection of patients	Withdrawals after run-in phase (n=27) due to refusal, poor comprehension or poor compliance, technical problems, equipment failure or GP advice
Age, gender and ethnicity	Age - Median (range): Symptoms group: 12 (7–14); PEF group: 11 (7–14) years. Gender (M:F): 48:42. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	(n=44) Intervention 1: Monitoring lung function + treatment - Monitoring PEF + treatment. Group PF based on symptoms plus PEF. A written symptom diary was completed each morning, and spirometry was performed twice daily. The spirometers of those children randomized to the PF group were reprogrammed so that the PEF value for any maneuver (but not other spirometric values) was visible to them at any time. The child and the main caregiver were taught self-management at a training session, which also included training in spirometry and symptom recording and which lasted 30–90 minutes according to need. A printed plan incorporating the child's own medication regime was color coded: green, PEF more than 70%, few symptoms (carry on as usual); yellow, PEF 50–70% after beta2 agonist (double-inhaled corticosteroid as well as taking additional beta2-agonist therapy); and red, PEF less than 50% after taking additional inhaled beta2 agonist, severe symptoms (commence oral prednisolone and/or seek medical help). The PEF levels for action were based on the child's best previous PEF.. Duration 12 weeks. Concurrent medication/care: Not stated Further details: 1. Additional education training :

	(n=46) Intervention 2: No lung function monitoring + treatment - Monitoring symptoms + treatment. Group S based on symptoms alone; the S group did not have access to any lung function results throughout the study.. Duration 12 weeks. Concurrent medication/care: Not stated Further details: 1. Additional education training :
Funding	Study funded by industry (United Kingdom National Asthma Campaign and Glaxo SmithKline, United Kingdom.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING PEF + TREATMENT versus MONITORING SYMPTOMS + TREATMENT Protocol outcome 1: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment - Actual outcome for Children 5 -<16 : Emergency GP visits at 12 weeks; Group 1: 10/44, Group 2: 11/45; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children 5 -<16 : Hospital admissions at 12 weeks; Group 1: 1/44, Group 2: 0/45; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children 5 -<16 : Attendance at A&E at 12 weeks; Group 1: 1/44, Group 2: 0/45; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Lung Function at End of Treatment - Actual outcome for Children 5 -<16 : FEV1 at 12 weeks; Group 1: mean 87.3 % of best value (SD 1.33); n=44, Group 2: mean 86.9 % of best value (SD 1.54); n=45; Percentage 0-100% Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children 5 -<16 : PEF at 12 weeks; Group 1: mean 83.4 % (SD 1.39); n=44, Group 2: mean 80.6 % (SD 1.74); n=45; Percentage 0-100% Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Symptom free days at End of Treatment - Actual outcome for Children 5 -<16 : Proportion of symptom-free days at 12 weeks; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Time of school/work at End of Treatment - Actual outcome for Children 5 -<16 : Time off school at 12 weeks; Group 1: 15/44, Group 2: 13/45; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; Exacerbation (need for OCS) at End of treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment

Table 130: Yoos 2002[1940]

Study	**Yoos 2002[1940]**

Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=168)
Countries and setting	Conducted in USA; Setting: 11 primary care settings
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: All school-aged children who carried a diagnosis of asthma
Stratum	Children 5 -<16 : Aged 6-19 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 6-19 years with a diagnosis of asthma, more that 3 asthma-related healthcare visits in the previous 12 months, English speaking, the child had not used a PEF meter in the previous 6 months.
Exclusion criteria	Children with mild asthma who were rarely symptomatic (had not had more than 3 asthma related healthcare visits in the previous 12 months).
Recruitment/selection of patients	All school-aged children who carried a diagnosis of asthma identified through computerised data sets.
Age, gender and ethnicity	Age - Range: 6-19 years. Gender (M:F): 99/69. Ethnicity:
Further population details	
Indirectness of population	No indirectness
Interventions	(n=57) Intervention 1: Monitoring lung function + treatment - Monitoring PEF and symptoms + treatment. Personal action plan zones based on symptoms and PEF. Green zone, yellow zone (rescue medication) and red zone (contact healthcare provider).. Duration 3 months. Concurrent medication/care: Both groups received asthma education and a personal action plan. Two week run-in period with allocated self-management method and at the end of this period the nurse estabilised zones based on PEF best and developed a personal action plan based on PEF and symptoms. Further details: 1. Additional education training : Additional education in both groups (n=56) Intervention 2: No lung function monitoring + treatment - Monitoring symptoms + treatment. Personal action plan zones based on symptoms only. Green zone, yellow zone (rescue medication) and red zone (contact healthcare provider).. Duration 3 months. Concurrent medication/care: Both groups received asthma education and a personal action plan.Two week run-in period with allocated self-management method and at the end of this period the nurse estabilised zones based on symptoms and developed a personal action plan based on symptoms. Further details: 1. Additional education training : Additional education in both groups

Funding	Academic or government funding (Supported by NIH grants)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING PEF AND SYMPTOMS + TREATMENT versus MONITORING SYMPTOMS + TREATMENT Protocol outcome 1: Lung Function at End of Treatment - Actual outcome for Children 5 -<16 : FEV1 % predicted at 3 months; Group 1: mean 88 % (SD 20.6); n=57, Group 2: mean 90 % (SD 21); n=56; FEV1 %pred 0-100 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; Exacerbation (need for OCS) at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

G.17 FeNO to monitor asthma control

Table 131: Calhoun 2012[264]

Study	**BASALT trail trial: Calhoun 2012[264]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=342)
Countries and setting	Conducted in USA; Setting: Secondary - adjustments of inhalled corticosteroids made at outpatient visits
Line of therapy	Mixed line
Duration of study	Intervention time: 9 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: All patients had a physician diagnosis of asthma, and either reversible airflow limitation (≥12% improvement in forced expiratory volume in the first second of expiration [FEV1] after 360 mcg of albuterol), or airway hyperresponsiveness (provocative concentration of methacholine [<8mg/ml] causing a 20% drop in FEV1)
Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Mild to moderate persistent asthma, acceptable control of asthma (i.e. a score of 0 or 1 on each of the 3

	questions on the Asthma Evaluation Questionnaire and predicted bronchodilator FEV1 >70%), and patients who demonstrated at least 75% adherence (i.e. those patients that could tolerate 2 puffs twice daily of beclomethasone HFA (40 mch/puff)) during the run-in period
Exclusion criteria	Poorly controlled, severe asthma
Recruitment/selection of patients	Participants were recruited cooperatively with a concurrent Asthma Clinical Research Network trial
Age, gender and ethnicity	Age - Mean (SD): 35 (11.83). Gender (M:F): 105/237. Ethnicity: White: 216, Black: 69, Hispanic: 38, Asian/Pacific Islander:13, Other: 5, American Indian/Alaska Native: 1
Further population details	
Indirectness of population	No indirectness
Interventions	(n=114) Intervention 1: No FeNO monitoring + treatment - Monitoring symptoms and lung function + treatment. Dose of inhaled coriticosteroids was adjusted by an investigator according to a strategy based on National Heart, Lung, and Blood Institute guidelines (PABA). Dose adjustments of inhaled corticosteroids were made at the time of clinic visits (every 6 weeks). Treatment step down - PABA: Physician assessment-based adjustment, inhaler A (1). Fev1 ≥85% at baseline, plus symptoms in past 2 wk ≤2 d/wk (all AEQ of 0); control status: well controlled; inhaler dose change: down 1 level. (2). Fev1 ≥85% at baseline, plus symptoms no worse than mild (AEQ scores of 0 or 1 on each question); control status: controlled; inhaler dose change: maintain current level. (3). Fev1 <85% at baseline, moderate symptoms (any AEQ score of 2 or 3), or meets criteria for treatment failure; control status: under controlled; inhaler dose change: up 1 level. . Duration 9 months. Concurrent medication/care: During the prerandomisation period, patients were given 3 inhalers coded as A, B, and C. Inhaler A contained beclomethasone HFA (40 mcg/puff), and inhalers B and C contained placebo. An albuterol inhaler was provided for use as needed for asthma symptoms. Participants were instructed to use 2 puffs twice daily from inhalers A and B, and to use 2 puffs from inhaler C each time they used 2 puffs of albuterol for symptom relief. Participants who demonstrated 75% adherence were randomised to one of the adjustment strategies (PABA, BBA, or SBA (occurrence of symptoms - data not extracted)). Beclomethasone HFA was provided at a dosage of 2 puffs twice daily (40 mcg/puff) before randomisation, corresponding to level 3 treatment. Hence, inhaled corticosteroid therapy could be intensified or deintensified during the trail. Following randomisation, beclomethasone HFA was contained only in inhaler A for PABA participants, only in inhaler B for BBA patients, and only in inhaler C for SBA participants. Thereafter, inhalers were adjusted according to the strategy assigned (i.e. PABA or BBA). Subsequent visits occurred at 2, 4, 6, 12, 18, 24, 30, and 36 weeks after randomisation. Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Aim to decrease ICS in controlled patients (To evaluate different approaches to dose adjustment of inhaled corticosteroids in a 3-group trial during 9 months in adults with mild to moderate asthma that was well controlled with low-dose inhaled corticosteroids).

	(n=115) Intervention 2: Monitoring FeNO + treatment. Dose of inhaled coriticosteroids was adjusted by an investigator according to exhaled nitric oxide (BBA). Dose adjustments of inhaled corticosteroids were made at the time of clinic visits (every 6 weeks). BBA: Biomarker-based adjustment, inhaler B. Fraction of exhaled nitric oxide, ppb: (1). <22; control status: well controlled; inhaler dose change: down 1 level. (2). 22-35; control status: controlled; inhaler dose change: maintain current level. (3). >35; control status: under controlled; inhaler dose change: up 1 level. Inhaled corticosteroids dose level: (1) none, na; (2) 80 (2 puffs), once daily (am); (3) 160 (2 puffs), twice daily; (4) 320 (4 puffs), twice daily; (5) 640 (8; 4 puffs at double strength), twice daily.. Duration 9 months. Concurrent medication/care: During the prerandomisation period, patients were given 3 inhalers coded as A, B, and C. Inhaler A contained beclomethasone HFA (40 mcg/puff), and inhalers B and C contained placebo. An albuterol inhaler was provided for use as needed for asthma symptoms. Participants were instructed to use 2 puffs twice daily from inhalers A and B, and to use 2 puffs from inhaler C each time they used 2 puffs of albuterol for symptom relief. Participants who demonstrated 75% adherence were randomised to one of the adjustment strategies (PABA, BBA, or SBA (occurrence of symptoms - data not extracted)). Beclomethasone HFA was provided at a dosage of 2 puffs twice daily (40 mcg/puff) before randomisation, corresponding to level 3 treatment. Hence, inhaled corticosteroid therapy could be intensified or deintensified during the trail. Following randomisation, beclomethasone HFA was contained only in inhaler A for PABA participants, only in inhaler B for BBA patients, and only in inhaler C for SBA participants. Thereafter, inhalers were adjusted according to the strategy assigned (i.e. PABA or BBA). Subsequent visits occurred at 2, 4, 6, 12, 18, 24, 30, and 36 weeks after randomisation. Further details: 1. Additional education training : Not applicable / Not stated / Unclear 2. Aim of intervention: Aim to decrease ICS in controlled patients (To evaluate different approaches to dose adjustment of inhaled corticosteroids in a 3-group trial during 9 months in adults with mild to moderate asthma that was well controlled with low-dose inhaled corticosteroids).
Funding	Academic or government funding (Study was conducted with the support of the Institute for Translational Sciences at the University of Texas Medical Branch, supported in part by a Clinical and Translational Science Award from the National Center for Advancing Translational Sciences, National Institutes of Health. The study was also supported by National Institutes of Health grants that were awarded by the National Heart, Lung, and Blood Institute. Teva Pharmaceuticals provided the study drug and matching placebo.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING FENO + TREATMENT versus MONITORING SYMPTOMS AND LUNG FUNCTION + TREATMENT Protocol outcome 1: Quality of life at End of treatment	

- Actual outcome for Adults and young people (16 years and over): AQLQ at 9 months; MD 0.00 (SE 0.11); Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Exacerbation (need for OCS) at End of treatment - Actual outcome for Adults and young people (16 years and over): Asthma exacerbation (including multiple epsiodes) at 36 weeks; HR lnHR -0.095 (SE 0.429); Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Asthma control questionnaires at End of Treatment - Actual outcome for Adults and young people (16 years and over): ACQ at 9 months; MD -0.04 (SE 0.08); Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 4: Rescue medication at End of Treatment - Actual outcome for Adults and young people (16 years and over): Rescue medication - albuterold rescue use (puffs) at 9 months; MD -0.06 (SE 0.034119); Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 5: Dose of regular asthma treatment (SABA, ICS) at End of Treatment - Actual outcome for Adults and young people (16 years and over): Dose of regular asthma therapy (ICS, beclomethasone HFA (40 mcg/puff)) at 36 weeks; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 6: Lung Function at End of Treatment - Actual outcome for Adults and young people (16 years and over): Lung function - am peak flow 2-week average prior to visit 4, L/min at 9 months; MD 2.3 (SE 7.2); Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people (16 years and over): Lung function - pm peak flow 2-week average prior to visit 4, L/min at 9 months; MD 3.8 (SE 7.04); Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people (16 years and over): Lung function - prebronchodilator FEV1 at 9 months; MD 0.98 (SE 0.96); Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 7: Time of school/work at End of Treatment - Actual outcome for Adults and young people (16 years and over): Time off school/work (no. of patients) at 36 weeks; OR lnOR 0.693 (SE 0.273); Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Symptom free days at End of Treatment

Table 132: de Jongste 2009[397]

Study	CHARISM (Children with Asthma subjected to Respiratory Inflammatory Status Monitoring) trial: De jongste 2009[397]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=151)
Countries and setting	Conducted in Netherlands; Setting: Secondary (clinic visits, data transmitted daily to centre, telephone contact).
Line of therapy	Mixed line
Duration of study	Intervention time: 30 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosed according to GINA guidelines
Stratum	Children 5 -<16
Subgroup analysis within study	Not applicable
Inclusion criteria	Age: 6-18 years; stable mild-moderate atopic asthma, diagnosed according to GINA guidelines; treatment with 200-1000 mcg of inhaled budesonide or equivalent daily for 2 months before randomisation; and RAST class 2 or higher or a positive skin prick test for at least one airborne allergen.
Exclusion criteria	Exclusion criteria were as follows: active smoking, previous admission to an intensive care unit for asthma, and concomitant disease that might affect FeNO.
Recruitment/selection of patients	Participants were recruited from 5 academic centres and 12 general hospitals.
Age, gender and ethnicity	Age - Mean (SD): 11.7 (3.538). Gender (M:F): 100/51. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	(n=77) Intervention 1: Monitoring FeNO + treatment - Monitoring FeNO and symptoms + treatment. Children in the FeNO group received an airway inflammation monitor (NIOX MINO; Aerocrine, Solna, Sweden) that measures FeNO. Measurements were performed daily. Measurement time was recorded by the device. Data was transmitted to the coordinating centre. All parents were phoned every 3 weeks between visits, and medication was adapted according to geometric mean FeNO over the preceding 3 weeks and cumulative symptom scores. Algorithm: (a) symptom score, high; FeNO, high; adjustment, increase; (b) symptom score, high; FeNO, low; adjustment, no change; (c) symptom score, low; FeNO, high; adjustment, increase; (d) symptom score, low; FeNO, low; adjustment, decrease or discontinue. Cut-off level for symptom score - high score: >60, low score ≤60 cumulative in 3 weeks. Cut-off levels for FeNO were 20 ppb for children aged 6-10 years and 25 ppb for older children. . Duration 30 weeks. Concurrent medication/care: Monitored children with atopic asthma for 30 weeks. Children were randomised at first visit, stratified by centre. ICS doses were adjusted every 3 weeks on the basis of either FeNO and symptoms, or symptom

	scores alone. All children recorded asthma symptoms in a palmtop diary. Entries were transmitted daily to the coordinating centre. Children in both groups were seen at randomisation and at 3, 12, 21, and 30 weeks. Doses were changed according to predefined steps for each type of inhaled steroid, for example, budesonide at 100, 200, 400, 800, and 1,200 mcg. Maximal allowed dose: 1200 mcg of budesonide or equivalent. If a combination of ICS and long-acting beta-agonist (LABA) was used, the LABA was stopped whenever decrease was required at the lowest ICS dose, before stopping ICS. Steroids were stopped for 6 weeks with low symptom scores at the lowest steroid dose level. Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Not applicable / Not stated / Unclear (n=74) Intervention 2: No FeNO monitoring + treatment - Monitoring symptoms + treatment. All parents were phoned every 3 weeks between visits. Algorithm: symptom score: above average (adjustment - increase); in range (no change); below range (decrease or discontinue). Cut-off level: the "normal range" was 10-60. Duration 30 weeks. Concurrent medication/care: Monitored children with atopic asthma for 30 weeks. Children were randomised at first visit, stratified by centre. ICS doses were adjusted every 3 weeks on the basis of either FeNO and symptoms, or symptom scores alone. All children recorded asthma symptoms in a palmtop diary. Entries were transmitted daily to the coordinating centre. Children in both groups were seen at randomisation and at 3, 12, 21, and 30 weeks. Doses were changed according to predefined steps for each type of inhaled steroid, for example, budesonide at 100, 200, 400, 800, and 1,200 mcg. Maximal allowed dose: 1200 mcg of budesonide or equivalent. If a combination of ICS and long-acting beta-agonist (LABA) was used, the LABA was stopped whenever decrease was required at the lowest ICS dose, before stopping ICS. Steroids were stopped for 6 weeks with low symptom scores at the lowest steroid dose level. Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Not applicable / Not stated / Unclear
Funding	Study funded by industry (Supported by a research grant from Aerocrine AB (Solna, Sweden). Conflict of interest statement: authors received travel grants, research grants and lectured at scientific meetings for the following: GlaxoSmithLine, Merck Sharp & Dohme, Altana Pharma, Aerocrine, Abbott, Valeas, Chiesi and Roche. Also note that the Department of Paediatrics/Erasmus MC Holding received research grants from GlaxoSmithKline, AstraZeneca, Aerocrine, Roche, Freisland Foods, Transave, Chiron, and Pfizer.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING FENO AND SYMPTOMS + TREATMENT versus MONITORING SYMPTOMS + TREATMENT

Protocol outcome 1: Quality of life at End of treatment
- Actual outcome for Children 5 -<16 : PACQLQ(S) - Paediatric Asthma Caregiver Quality of Life Questionnaire with Standardised Activities at 30 weeks; Group 1: mean

6.2 (SD 0.8); n=75, Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Exacerbation (need for OCS) at End of treatment - Actual outcome for Children 5 -<16 : Exacerbation - OCS, prednisone course at 30 weeks; Group 1: 9/75, Group 2: 12/72; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment - Actual outcome for Children 5 -<16 : UHU at 30 weeks; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 4: Rescue medication at End of Treatment - Actual outcome for Children 5 -<16 : Rescue medication - beta agonist puffs per 3 weeks at 30 weeks; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 5: Dose of regular asthma treatment (SABA, ICS) at End of Treatment - Actual outcome for Children 5 -<16 : Dose of regular therapy - ICS, budesonide at 30 weeks; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 6: Lung Function at End of Treatment - Actual outcome for Children 5 -<16 : Lung function - FEV1 at 30 weeks; Group 1: mean 95 % (SD 14); n=75, Group 2: mean 94 % (SD 14); n=72; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 7: Symptom free days at End of Treatment - Actual outcome for Children 5 -<16 : % symptom free days over last 12 weeks at 30 weeks; MD 0.3 (95%CI -10 to 11); Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Asthma control questionnaires at End of Treatment; Time of school/work at End of Treatment

Table 133: Fritsch 2006[522]

Study	**Fritsch 2006[522]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=47)
Countries and setting	Conducted in Austria; Setting: Secondary care - Paediatric Pulmonology outpatient clinic
Line of therapy	Mixed line
Duration of study	Intervention time: 6 months

Method of assessment of guideline condition	Adequate method of assessment/diagnosis: A paediatrician, trained in paediatric pulmonology and allergology, diagnosed participants asthma according to ATS criteria.
Stratum	Children 5 -<16
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 6-18 years, with mild to moderate persistent asthma. All participants had a positive skin prick test or radioallergosorbent test (RAST >1) to at least one of seven common aeroallergens (cat, dog, house dust mite, alternaria, birch-, hazelnut-, and mixed grass-pollen) in their past medical history or at the time of recruitment.
Exclusion criteria	Participants who had received oral or IV steroid treatment 4 weeks prior to the first visit were excluded from the study.
Recruitment/selection of patients	Recruited from the Paediatric Pulmonology outpatient clinic of the University Children's Hospital Vienna.
Age, gender and ethnicity	Age - Mean (SD): 11.73 (3.121). Gender (M:F): 28/19. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: No FeNO monitoring + treatment - Monitoring symptoms and lung function + treatment. Children in the control group were treated considering parameters of asthma control (symptoms, short-acting beta agonist use, and lung function) recommended in current asthma guidelines. A step down in therapy was performed if FEV1 % predicted was ≥80% and there was no or mild symptoms over the last 4 weeks and beta agonist use was <6 puffs over the last 12 days. A step up was performed in every other case. . Duration 6 months. Concurrent medication/care: Following a run-in period of 4 weeks participants were randomly assigned to a control group or a FeNO group at the first visit. The trail included five visits (6 weeks intervals) over a period of 6 months. Doses - Low dose ICS: (2X 100 mcg fluticasone or 2x 200 mcg budesonide); Low dose ICS + leukotriene receptor agonists: (2x 100 mcg fluticasone or 2x 200 mcg budesonide + 5 mg montelukast once daily p.o.); Low dose ICS + long acting beta-agonist (2x 100 mcg fluticasone + 2x 50 mcg salmeterol or 2x 200 mcg Budesonide + 2x 12 mcg formeterol); High dose ICS + leukotriene receptor agonist (2x 250 mcg fluticasone or budesonide 2x 400 mcg + 1 daily 5 mg montelukast p.o.); High dose ICS + long acting beta-agonist (2x 250 mcg fluticasone + 2x 50 mcg salmeterol or 2x 400 mcg budesonide + 2x 12 mcg formeterol). Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Not applicable / Not stated / Unclear (n=22) Intervention 2: Monitoring FeNO + treatment - Monitoring FeNO, symptoms and lung function + treatment. FeNO group therapy was based on symptoms, beta agonist use, lung function, and FeNO. A step down in therapy was performed if FEV1 % predicted was ≥80% and there was no or mild symptoms over the last 4 weeks and beta agonist use was <6 puffs over the last 14 days. A step up was performed in every other case. Treatment was further adjusted

	according the FeNO cut-off point, >20 ppb. In participants with stable asthma increased FeNO was considered a sign of insufficient anti-inflammatory treatment. These patients were provided with 2-week diary cards to record daily symptoms, beta agonists use and controller medication requirement, and telephone calls were regularly performed to check adherence to therapy. Asymptomatic patients on therapy with beta-agonist on demand only, with normal lung function but increased FeNO were prescribed low dose steroids. Step up was performed irrespective of FeNO level if FEV1% predicted was <80% and/or there were severe symptoms over the last 4 weeks and/or beta-agonist use was ≥6 puffs over the last 14 days. If FeNO was raised in these patients, they received 2-week diary cards as well. Step down was performed if FEV1% predicted was ≥80% and there were no or mild symptoms over the last 4 weeks and beta-agonist use was <6 puffs over the last 14 days and FeNO was ≤20 ppb.. Duration 6 months. Concurrent medication/care: Following a run-in period of 4 weeks participants were randomly assigned to a control group or a FeNO group at the first visit. The trail included five visits (6 weeks intervals) over a period of 6 months. Doses - Low dose ICS: (2X 100 mcg fluticasone or 2x 200 mcg budesonide); Low dose ICS + leukotriene receptor agonists: (2x 100 mcg fluticasone or 2x 200 mcg budesonide + 5 mg montelukast once daily p.o.); Low dose ICS + long acting beta-agonist (2x 100 mcg fluticasone + 2x 50 mcg salmeterol or 2x 200 mcg Budesonide + 2x 12 mcg formeterol); High dose ICS + leukotriene receptor agonist (2x 250 mcg fluticasone or budesonide 2x 400 mcg + 1 daily 5 mg montelukast p.o.); High dose ICS + long acting beta-agonist (2x 250 mcg fluticasone + 2x 50 mcg salmeterol or 2x 400 mcg budesonide + 2x 12 mcg formeterol). Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Not applicable / Not stated / Unclear
Funding	Study funded by industry (Aerocine provided technical support and help with data analyses)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING FENO, SYMPTOMS AND LUNG FUNCTION + TREATMENT versus MONITORING SYMPTOMS AND LUNG FUNCTION + TREATMENT Protocol outcome 1: Exacerbation (need for OCS) at End of treatment - Actual outcome for Children 5 -<16 : Exacerbation - OCS at 6 months; Group 1: 2/22, Group 2: 2/25; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Dose of regular asthma treatment (SABA, ICS) at End of Treatment - Actual outcome for Children 5 -<16 : Dose of regular treatment - ICS dose at 6 months; Other: ; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Lung Function at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Table 134: Honkoop 2014[691]

Study	Asthma Control Cost-Utility Randomised Trial Evaluation (ACCURATE) trial: Honkoop 2014[691]
Study type	RCT (Cluster randomised; Parallel)
Number of studies (number of participants)	1 (n=647)
Countries and setting	Conducted in Netherlands; Setting: Primary
Line of therapy	Mixed line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Doctor diagnosed asthma according to Dutch national guidelines
Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	18-50 years old, doctor-diagnosed asthma according to the Dutch national guidelines, a prescription for ICSs for at least 3 months in the previous year, and asthma being managed in primary care
Exclusion criteria	Significant comorbidity (at the GPs discretion), inability to understand Dutch, and a prescription for oral corticosteroids in the previous month
Recruitment/selection of patients	General practices from both rural and urban areas in The Netherlands were invited to participate
Age, gender and ethnicity	Age - Mean (SD): 39.42 (9.633). Gender (M:F): 191/420 . Ethnicity: Not specified
Further population details	
Indirectness of population	No indirectness
Interventions	(n=205) Intervention 1: Monitoring FeNO + treatment - Monitoring FeNO and symptoms + treatment. Treatment strategy: aiming at FeNO-driven controlled asthma (FCa strategy). In all strategies, patients visited the practice nurse of their general practice every 3 months over the course of 1 year. During these visits, the practice nurse assessed current medication use and asthma control status by using the 7-item asthma control questionnaire that includes lung function. In addition, FeNO measurement was performed in the FCa strategy. Duration 12 months. Concurrent medication/care: At each visit, a patient's asthma control status was classified based on the ACQ score as controlled (ACQ score ≤0.75), partly controlled (0.75 <ACQ ≤1.5), or uncontrolled (ACQ score >1.5); and additionally in the FCa strategy as 3 subcategories of FeNO: low/absence of airway inflammation for values at 25 ppb or less, intermediate at 26 to 50 ppb, and high/presence of airway inflammation at greater than 50 ppb. Treatment decisions were based on a dedicated algorithm for each strategy. (1)Strategy aimed at Ca = asthma controlled status Ca (ACQ ≤0.75): 3mo: no change, 6mo: step down; asthma controlled status PCa (0.75 > ACQ ≤1.5): step up, treatment choice open; asthma

	controlled status uncontrolled (ACQ >1.5): step up, treatment choice open. (2)Strategy aimed at FCa, low FeNO (<25 ppb) = asthma controlled status Ca (ACQ ≤0.75): step down, treatment choice open; asthma controlled status PCa (0.75 > ACQ ≤1.5): 3 mo: no change/change within current step to LABA, 6mo: step down to ICS; asthma controlled status uncontrolled (ACQ >1.5): 3 mo: step up LABA, 6mo: revise asthma diagnosis. (3)Strategy aimed at FCa, intermediate FeNO (25-50 ppb) = asthma controlled status Ca (ACQ ≤0.75): no change; asthma controlled status PCa (0.75 > ACQ ≤1.5): step up, treatment choice open; asthma controlled status uncontrolled (ACQ >1.5): treatment choice open. (4)Strategy aimed at FCa, high FeNO (>50 ppb) = asthma controlled status Ca (ACQ ≤0.75): step up/change within current step to ICS; asthma controlled status PCa (0.75 > ACQ ≤1.5): step up, 1 X ICS; asthma controlled status uncontrolled (ACQ >1.5): step up, 2 X ICS. Current medication use and all measurements were entered into an online decision support tool, which subsequently automatically generated treatment advice based on the appropriate algorithm for each of the treatment strategies. Patients' current medication use was classified as an asthma treatment step ranging from 0 (only short-acting beta agonists) to 5 (oral prednisone) based on the US National Asthma Education and Prevention Programe guideline. When treatment was to be adjusted, in the Ca strategy professionals and patients could choose any (combination of) type or types of asthma medication they preferred within a certain treatment step, whereas the FCa strategy offered more guidance toward adding/removing LABAS or ICSs. Further details: 1. Additional education training : No education in both groups 2. Aim of intervention: Not applicable / Not stated / Unclear (n=210) Intervention 2: No FeNO monitoring + treatment - Monitoring symptom control questionnaires + treatment. Treatment strategy: aiming at controlled asthma (Ca strategy). In all strategies, patients visited the practice nurse of their general practice every 3 months over the course of 1 year. During these visits, the practice nurse assessed current medication use and asthma control status by using the 7-item asthma control questionnaire that includes lung function. . Duration 12 months. Concurrent medication/care: At each visit, a patient's asthma control status was classified based on the ACQ score as controlled (ACQ score ≤0.75), partly controlled (0.75 <ACQ ≤1.5), or uncontrolled (ACQ score >1.5); and additionally in the FCa strategy as 3 subcategories of FeNO: low/absence of airway inflammation for values at 25 ppb or less, intermediate at 26 to 50 ppb, and high/presence of airway inflammation at greater than 50 ppb. Treatment decisions were based on a dedicated algorithm for each strategy. (1)Strategy aimed at Ca = asthma controlled status Ca (ACQ ≤0.75): 3mo: no change, 6mo: step down; asthma controlled status PCa (0.75 > ACQ ≤1.5): step up, treatment choice open; asthma controlled status uncontrolled (ACQ >1.5): step up, treatment choice open. (2)Strategy aimed at FCa, low FeNO (<25 ppb) = asthma controlled status Ca (ACQ ≤0.75): step down, treatment choice open; asthma controlled status PCa (0.75 > ACQ ≤1.5): 3 mo: no change/change within current step to LABA, 6mo: step down to ICS; asthma controlled status uncontrolled (ACQ >1.5): 3 mo: step up LABA, 6mo: revise asthma diagnosis. (3)Strategy aimed at FCa, intermediate FeNO (25-50 ppb) = asthma controlled status Ca (ACQ ≤0.75): no change; asthma controlled status PCa (0.75 > ACQ ≤1.5): step up, treatment choice open; asthma controlled status uncontrolled (ACQ >1.5): treatment choice open. (4)Strategy aimed at FCa, high FeNO (>50 ppb) =

	asthma controlled status Ca (ACQ ≤0.75): step up/change within current step to ICS; asthma controlled status PCa (0.75 > ACQ ≤1.5): step up, 1 X ICS; asthma controlled status uncontrolled (ACQ >1.5): step up, 2 X ICS. Current medication use and all measurements were entered into an online decision support tool, which subsequently automatically generated treatment advice based on the appropriate algorithm for each of the treatment strategies. Patients' current medication use was classified as an asthma treatment step ranging from 0 (only short-acting beta agonists) to 5 (oral prednisone) based on the US National Asthma Education and Prevention Programe guideline. When treatment was to be adjusted, in the Ca strategy professionals and patients could choose any (combination of) type or types of asthma medication they preferred within a certain treatment step, whereas the FCa strategy offered more guidance toward adding/removing LABAs or ICSs. Further details: 1. Additional education training: No education in both groups 2. Aim of intervention: Not applicable / Not stated / Unclear
Funding	Study funded by industry (Study was funded by the Netherlands Organisation for Health Research and Development and the Netherlands Asthma Foundation, and nonfinancial support was received from Aerocrine. Author holds stock in Grace Bros and received consultancy fees from Astra-Zeneca, GlaxoSmithKline, and Novartis, as well as grants funding from ACME Pharmaceutical.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING FENO AND SYMPTOMS + TREATMENT versus MONITORING SYMPTOM CONTROL QUESTIONNAIRES + TREATMENT

Protocol outcome 1: Exacerbation (need for OCS) at End of treatment
- Actual outcome for Adults and young people (16 years and over): Exacerbation (severe, defined as hospitalisation, emergency care or use of OCS) at 12 months; Risk of bias: High; Indirectness of outcome: Serious indirectness

Protocol outcome 2: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment
- Actual outcome for Adults and young people (16 years and over): UHU - hospitalisation (from the exacerbation outcome) at 12 months; Group 1: 1/189, Group 2: 2/203; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults and young people (16 years and over): UHU - ED visit (from the exacerbation outcome) at 12 months; Group 1: 2/189, Group 2: 3/203; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Asthma control questionnaires at End of Treatment
- Actual outcome for Adults and young people (16 years and over): ACQ-7 score at 12 months; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Lung Function at End of Treatment
- Actual outcome for Adults and young people (16 years and over): Lung function (FEV1 % predicted) at 12 months; Risk of bias: High; Indirectness of outcome: No

indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Table 135: Peirsman 2013[1317]

Study	**Peirsman 2013[1317]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=99)
Countries and setting	Conducted in Belgium; Setting: Secondary
Line of therapy	Mixed line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: Not stated - children with persistent allergic asthma
Stratum	Children 5 -<16
Subgroup analysis within study	Not applicable
Inclusion criteria	Children with persistent allergic asthma. Mild to severe persistent asthma according to GINA guidelines, for a period of at least 6 months, and allergic sensitisation (i.e., a positive skin prick test and/or specific IgE antibodies against nihalant allergens).
Exclusion criteria	Exclusion criteria comprised significant comorbidity, an acute exacerbation or the administration of experimental medication 4 weeks prior to the screening visit, hospitalisation and/or systematic corticosteroids 12 weeks prior to the screening visit or oral corticosteroids dependence.
Recruitment/selection of patients	Secondary - visits were organised by physicians from seven Belgian hospitals.
Age, gender and ethnicity	Age - Mean (SD): 10.65 (2.151). Gender (M:F): 66/33. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	(n=49) Intervention 1: Monitoring FeNO and symptoms + treatment. In the intervention group, FeNO measurements were primarily used to adjust the treatment. Goal was to keep FeNO below 20 ppb, the rounded 95% upper limit of

	FeNO values in healthy children, deduced from previous trials. Controlled asthma = NO ≤20 ppb and controlled; ICS (dosage in budesonide or equivalent) = ICS step down - 100 mcg/day, below 100 mcg/day: stop and add LTRA; LTRA = stay the same; ICS + LTRA = ICS step down: -100 mcg/day, below 100 mcg/day: stop ICS; ICS + LABA = stop LABA. Partly controlled asthma = NO ≤20 ppb and partly controlled or uncontrolled; ICS (dosage in budesonide or equivalent) = consider + LTRA; consider + ICS 100 mcg/day (max 200 mcg/day); ICS + LTRA = consider ICS step up + 100 mcg/day (max 400 mcg/day, then add LABA); ICS + LABA = consider + LTRA. Uncontrolled asthma = NO >20 ppb regardless of symptoms; ICS (dosage in budesonide or equivalent) = +LTRA; LTRA = +ICS 100 mcg/day (max 200 mcg/day); ICS + LTRA = ICS step up: 100 mcg/day, (max 400 mcg/day, then add LABA); ICS + LABA = replace LABA with LTRA.. Duration 12 months. Concurrent medication/care: Five visits, one every 3 months. Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Not applicable / Not stated / Unclear (n=50) Intervention 2: No FeNO monitoring + treatment - Monitoring symptoms and lung function + treatment. In the control group, control and treatment adjustments during each visit were determined by the reporting of symptoms (i.e., limitation of activities, daytime and nocturnal symptoms), the need for rescue treatment during the two preceding weeks and spirometry (FEV1), based on GINA guidelines.. Duration 12 months. Concurrent medication/care: Five visits, one every 3 months. Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Not applicable / Not stated / Unclear
Funding	Study funded by industry (Research supported in part by a research grant from the Investigator Initiated Studies Program of Merck & Co., Inc. NO analysers were provided by Aerocrine, Solna, Sweden.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING FENO + TREATMENT versus MONITORING SYMPTOMS AND LUNG FUNCTION + TREATMENT

Protocol outcome 1: Exacerbation (need for OCS) at End of treatment
- Actual outcome for Children 5 -<16 : exacerbation (OCS) at 12 months; Group 1: 2/49, Group 2: 3/50; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment
- Actual outcome for Children 5 -<16 : UHU - number of unscheduled asthma-related contacts at 12 months; Group 1: 6/44, Group 2: 15/43; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Children 5 -<16 : UHU - number of children with ≥1 hospital admission at 12 months; Group 1: 1/43, Group 2: 1/43; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Children 5 -<16 : UHU - number of children with ≥1 emergency room admission at 12 months; Group 1: 2/45, Group 2: 4/46; Risk of bias: Very

high; Indirectness of outcome: No indirectness Protocol outcome 3: Dose of regular asthma treatment (SABA, ICS) at End of Treatment - Actual outcome for Children 5 -<16 : Dose of regular therapy - change in daily ICS dose at 12 months; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 4: Lung Function at End of Treatment - Actual outcome for Children 5 -<16 : lung function - FEV1 (mean % predicted) [≥6mo] at 12 months; Group 1: mean 93.9 mean % predicted (SD 15.5); n=49, Group 2: mean 91.2 mean % predicted (SD 12.3); n=50; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children 5 -<16 : lung function - FEV1 (mean % predicted) [<6mo] at 3 months; Group 1: mean 92.2 (SD 14.1); n=49, Group 2: mean 90.7 (SD 13.2); n=50; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 5: Symptom free days at End of Treatment - Actual outcome for Children 5 -<16 : % symptom free days at 12 months; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 6: Time of school/work at End of Treatment - Actual outcome for Children 5 -<16 : time off school/work - number of children missed school at 12 months; Group 1: 10/46, Group 2: 12/46; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment

Table 136: Petsky 2014[1340]

Study	**Petsky 2014[1340]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=63)
Countries and setting	Conducted in Australia, Hong Kong (China); Setting: Secondary care
Line of therapy	Unclear
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Under the care of a paediatrician
Stratum	Children 5 -<16
Subgroup analysis within study	Not applicable
Inclusion criteria	Children aged >4 years with persistent asthma, prescribed anti-inflammatory asthma treatment, and receiving their

	care primarily through the clinical service at Royal Children's Hospital, Brisbane or Prince of Wales Hospital, Hong Kong.
Exclusion criteria	Children who had underlying cardio-respiratory illness such as bronchiectasis or tracheomalacia, inability to take ICS or long acting beta-2-agonists (LABA) or previous poor adherence to medications (as documented in clinic notes).
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Median (IQR): 10.17 (6.56,12.69) years FeNO; 10.08 (6.25, 12.44) years controls. Gender (M:F): 31:32. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	(n=31) Intervention 1: Monitoring FeNO + treatment. Management based on FeNO levels and atopic status. If FeNO was low for two consecutive visits, medications were stepped down. Elevated FeNO was defined ≥10ppb in children with no positive skin prick test (SPT), ≥12ppb in children with one positive SPT, and ≥20ppb in children with ≥2 positive SPT. Treatment steps were modified from the Australian National Asthma Council guidelines and GINA guidelines.. Duration 1 year. Concurrent medication/care: 2-week run-in period when the children were maintained on their current treatment. If they were unstable (based on clinician review and diary cards) their medications were adjusted by their treating physician and a further run-in period was undertaken Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Not applicable / Not stated / Unclear (n=32) Intervention 2: No FeNO monitoring + treatment - Monitoring symptoms + treatment. Management based on clinical symptoms. Treatment decisions were made on symptoms as recorded on the asthma symptom diary card. Control was considered inadequate and treatment increased if scores increased by more than or equal to 15% since the previous visit. Treatment was stepped down if the child's scores totalled <10 in recent week. Treatment steps were modified from the Australian National Asthma Council guidelines and GINA guidelines.. Duration 1 year. Concurrent medication/care: 2-week run-in period when the children were maintained on their current treatment. If they were unstable (based on clinician review and diary cards) their medications were adjusted by their treating physician and a further run-in period was undertaken Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Not applicable / Not stated / Unclear
Funding	Academic or government funding (Asthma Foundation of Queensland 2008, Royal Children's Hospital Foundation, NHMRC)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING FENO + TREATMENT versus MONITORING SYMPTOMS + TREATMENT	

Protocol outcome 1: Quality of life at End of treatment - Actual outcome for Children 5 -<16 : Asthma QOL score at 12 months; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Exacerbation (need for OCS) at End of treatment - Actual outcome for Children 5 -<16 : 1 or more exacerbations at 12 months; Group 1: 6/27, Group 2: 15/28; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment - Actual outcome for Children 5 -<16 : Hospitalisation at 12 months; Group 1: 0/27, Group 2: 0/28; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Dose of regular asthma treatment (SABA, ICS) at End of Treatment - Actual outcome for Children 5 -<16 : Fluticasone dose at 12 months; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: Lung Function at End of Treatment - Actual outcome for Children 5 -<16 : FEV1 % predicted at 12 months; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Table 137: Pijnenburg 2005[1345]

Study	**Pijnenburg 2005[1345]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=85)
Countries and setting	Conducted in Netherlands
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: States participants were children with atopic asthma, and fulfilled ATS criteria for asthma.
Stratum	Children 5 -<16
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients had been using inhaled corticosteroids (ICS) at a constant dose for at least 3 months preceding the study. All

	patients were atopic, defined as RAST class 2 or higher for at least 1 airborne allergen ever.
Exclusion criteria	None specified.
Recruitment/selection of patients	Participants were recruited from the outpatient clinic of Erasmus MC - Sophia Children's Hospital.
Age, gender and ethnicity	Age - Mean (SD): 12.28 (2.868). Gender (M:F): 55/30. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	(n=42) Intervention 1: Monitoring FeNO + treatment - Monitoring FeNO and symptoms + treatment. In the intervention group, ICS doses were determined by FeNO and symptoms according to the following algorithm: FeNO >30ppb, regardless of symptoms = ICS increased; FeNO ≤30ppb AND symptoms > 14 = ICS stays same; FeNO ≤30 AND symptoms ≤14 = ICS decreased.. Duration 12 months. Concurrent medication/care: After a 2-week run-in period, participants were randomly allocated to one of two groups stratified for baseline FeNO (≥ 30 or <30 ppb) and dose of ICS (≥ 400 or <400 mcg budesonide or equivalent daily dose). Study duration was 12 months, with five visits at 3-month intervals. FeNO was measured at each visit, and the ICS dose was then adapted to FeNO and/or symptom scores recorded during the previous 2 weeks. Throughout the study, 2000 mcg per day budesonide (or equivalent dose of other ICS) was the maximum allowed dose. The study design was such that the patients' physician was allowed to deviate from the recommended ICS dose. Lung function and bronchoprovocation tests with methacholine were performed at visits 1 and 5. At all visits, inhaler technique was checked and optimised. ICS doses: 100 mcg: increase to 200 mcg, decrease to 0 mcg; 200 mcg: increase to 400 mcg, decrease to 100 mcg; 400 mcg: increase to 800 mcg, decrease to 200 mcg; 500 mcg: increase to 1000 mcg, decrease to 250 mcg; 800 mcg: increase to 1200 mcg, decrease to 400 mcg; 1000 mcg: increase to 1500 mcg, decrease to 500 mcg; 1200 mcg: increase to 1600 mcg, decrease to 800 mcg; 1600 mcg: increase to 2000 mcg, decrease to 1200 mcg; 2000 mcg: no further increase, decrease to 1000 mcg. Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Not applicable / Not stated / Unclear (n=47) Intervention 2: No FeNO monitoring + treatment - Monitoring symptoms + treatment. In the control group, only symptoms influenced ICS dosing. Symptoms >14 = ICS increased; symptoms ≤ 14, first time = ICS stays same; symptoms ≤14, second time = ICS decreased. . Duration 12 months. Concurrent medication/care: After a 2-week run-in period, participants were randomly allocated to one of two groups stratified for baseline FeNO (≥ 30 or <30 ppb) and dose of ICS (≥ 400 or <400 mcg budesonide or equivalent daily dose). Study duration was 12 months, with five visits at 3-month intervals. FeNO was measured at each visit, and the ICS dose was then adapted to FeNO and/or symptom scores recorded during the previous 2 weeks. Throughout the study, 2000 mcg per day budesonide (or equivalent dose of other ICS) was the maximum allowed dose. The study design was such that the patients' physician was allowed to deviate from the recommended ICS dose. Lung function and bronchoprovocation tests with

	methacholine were performed at visits 1 and 5. At all visits, inhaler technique was checked and optimised. ICS doses: 100 mcg: increase to 200 mcg, decrease to 0 mcg; 200 mcg: increase to 400 mcg, decrease to 100 mcg; 400 mcg: increase to 800 mcg, decrease to 200 mcg; 500 mcg: increase to 1000 mcg, decrease to 250 mcg; 800 mcg: increase to 1200 mcg, decrease to 400 mcg; 1000 mcg: increase to 1500 mcg, decrease to 500 mcg; 1200 mcg: increase to 1600 mcg, decrease to 800 mcg; 1600 mcg: increase to 2000 mcg, decrease to 1200 mcg; 2000 mcg: no further increase, decrease to 1000 mcg. Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Not applicable / Not stated / Unclear
Funding	Other (Supported by grant from the Kroger Foundation/Sophia Children's Hospital Foundation. Authors note in conflict of interest statement that the Department of Paediatrics of Erasmus University received research grants and payments for consultancy services from Aerocine (manufacturer of NO analysers).)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING FENO AND SYMPTOMS + TREATMENT versus MONITORING SYMPTOMS + TREATMENT Protocol outcome 1: Exacerbation (need for OCS) at End of treatment - Actual outcome for Children 5 -<16 : Exacerbation - need for OCS (prednisone course) at 12 months; Group 1: 7/39, Group 2: 10/46; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Dose of regular asthma treatment (SABA, ICS) at End of Treatment - Actual outcome for Children 5 -<16 : Dose of regular treatment (mean daily ICS dose score, at 3 months) at 3 months; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: Lung Function at End of Treatment - Actual outcome for Children 5 -<16 : Lung function - FEV1 at 12 months; MD 2.3 (95%CI -1.8 to 6.3); Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Table 138: Pike 2012[1346]

Study	Pike 2012[1346]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in United Kingdom; Setting: Secondary - hospital
Line of therapy	Mixed line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Asthma diagnosis was based upon a history of typical symptoms, ≥15% icreas i FEV1 wih bronchodilator or diurnal PEF variability of ≥15%.
Stratum	Children 5 -<16
Subgroup anaysis within study	Not applicable
Inclusion criteria	Participants were age 6-17 years, clinical diagnosis of asthma and treatment with ≥400 mcg/day beclomethasone/budesonide or ≥200 mcg/day fluticasone.
Exlusion criteria	Inability to preform spirometry or FeNO measurement, cigarette soking, poor treatment adherence, life-thretening excerbation or need for maintenance oral prednisolone.
Recruitment/election of patients	Participants were recruited from outpatient clinics at Southampton University Hospital; St Mary's Hospital, Portsmouth; St Mary's Hospital, Isle of Wight; and, the Royal Hampshire County Hospital, Winchester.
Age, gender and ethnicity	Age - Mean (SD): 10.98 (2.695). Gender (M:F): 51/39. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	(n=44) Intervention 1: No FeNO monitoring + treatment - Monitoring symptoms, BD use and lung function + treatment. Therapy decisions were taken by an independent clinician following a simple algorithm reflecting symptom control for standard management subjects. Under standard management, therapy was increased if symptoms were poorly controlled and decreased if symptoms were well controlled for 3 months as per the SIGN/BTS (Scottish Intercollegiate Guidelines Network/British Thoracic Society) guidelines. Algorithm for managing asthma: Standard management group: (a) poorly controlled asthma - increase inhaled corticosteroids or add LABA and/or LTRA as directed by stepwise approach to therapy SIGN/BTS; (b) asthma controlled – no change in inhaled corticosteroids; (c) well-controlled asthma – if well-controlled for 3 months reduced if inhaled corticosteroids if dose ≤400 mcg, reduce LABA.. Duration 12 months. Concurrent medication/care: Participants asthma was stabilised if necessary over 4-16 weeks prior to randomisation. Participants were assessed 2 monthly for 12 months. Participants' asthma was

	categorised as well controlled (symptoms and reliever inhaler <1 per week and FEV1 ≥90% predicted); controlled (symptoms or reliever inhaler use 1-2 days per week or FEV1 ≥80% predicted); or poorly controlled (symptoms or reliever inhaler use >2 days per week or FEV1 <80% predicted). Step 1: no inhaled corticosteroid (option 1); no inhaled corticosteroid (option 2); no inhaled corticosteroid (option 3). Step 2: Beclometasone 50 mcg twice a day via spacer (option 1); Budesonide 50 mcg twice a day via spacer (or tubohaler) (options 2); Fluticasone 50 mcg once a day via spacer (or accuhaler) (option 3). Step 3: Beclometasone 100 mcg twice a day via spacer (option 1); Budesonide 100 mcg twice a day via spacer (or tubohaler) (options 2); Fluticasone 50 mcg twice a day via spacer (or accuhaler) (option 3). Step 4: Beclometasone 200 mcg twice a day via spacer (option 1); Budesonide 200 mcg twice a day via spacer (or tubohaler) (options 2); Fluticasone 100 mcg once a day via spacer (or accuhaler) (option 3). Step 5: Trial of LABA, if ineffective consider trial of LTRA (options 1, 2, 3). Step 6: Fluticasone 125 mcg twice a day via spacer (options 1, 2, 3). Step 7: Fluticasone 250 mcg twice a day via spacer (options 1, 2, 3). Step 8: Consider a short course of prednisolone or other therapeutic options (options 1, 2, 3). Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Not applicable / Not stated / Unclear (n=46) Intervention 2: Monitoring FeNO + treatment - Monitoring FeNO and symptoms + treatment. Therapy decisions were taken by an independent clinician following a simple algorithm reflecting FeNO measurements in addition to symptom control for FeNO group. ICS was decreased if FeNO ≤15 ppb and symptoms were controlled or well controlled for 3 months in similar steps as for the standard management group. Where asthma was poorly controlled and FeNO was <25ppb in the FeNO group, long-acting beta-agonist (LABA) therapy was maximised before ICS was increased. ICS was increased if FeNO ≥25 ppb or FeNO doubled from baseline. If FeNO remained raised after increasing by two SIGN/BTS steps, ICS was not further increased unless participants were poorly controlled. Algorithm for managing asthma: FeNO group: (a) ≥25 ppb or FeNO more than twice baseline: poorly controlled asthma - increase inhaled corticosteroids or add LTRA if already at SIGN/BTS step 4 (if after increasing by two SIGN/BTS steps FeNO remains high do not increase therapy further); asthma controlled/well-controlled asthma – increase inhaled corticosteroids or add LTRA if already at SIGN/BTS step 4. (b) >15 to <25 ppb: poorly controlled asthma - increase LABA therapy (if dose maximal, increase corticosteroids or add LTRA if already at SIGN/BTS step 4); asthma controlled/well-controlled asthma – continue current treatment. (c) ≤15 ppb: poorly controlled asthma – increase LABA (if does maximal, increase corticosteroids or add LTRA if already at SIGN/BTS step 4); asthma controlled/well-controlled asthma – if asthma controlled for 3 months, reduce inhaled corticosteroids (if dose ≤400 mcg, reduce LABA).. Duration 12 months. Concurrent medication/care: Participants asthma was stabilised if necessary over 4-16 weeks prior to randomisation. Participants were assessed 2 monthly for 12 months. Participants' asthma was categorised as well controlled (symptoms and reliever inhaler <1 per week and FEV1 ≥90% predicted); controlled (symptoms or reliever inhaler use 1-2 days per week or FEV1 ≥80% predicted); or poorly controlled (symptoms or reliever inhaler use >2 days per week or FEV1 <80% predicted). Step 1: no inhaled corticosteroid (option 1); no inhaled corticosteroid (option 2); no inhaled corticosteroid (option 3). Step 2: Beclometasone 50 mcg twice a day via spacer

	(option 1); Budesonide 50 mcg twice a day via spacer (or tubohaler) (options 2); Fluticasone 50 mcg once a day via spacer (or accuhaler) (option 3). Step 3: Beclometasone 100 mcg twice a day via spacer (option 1); Budesonide 100 mcg twice a day via spacer (or tubohaler) (options 2); Fluticasone 50 mcg twice a day via spacer (or accuhaler) (option 3). Step 4: Beclometasone 200 mcg twice a day via spacer (option 1); Budesonide 200 mcg twice a day via spacer (or tubohaler) (options 2); Fluticasone 100 mcg once a day via spacer (or accuhaler) (option 3). Step 5: Trial of LABA, if ineffective consider trial of LTRA (options 1, 2, 3). Step 6: Fluticasone 125 mcg twice a day via spacer (options 1, 2, 3). Step 7: Fluticasone 250 mcg twice a day via spacer (options 1, 2, 3). Step 8: Consider a short course of prednisolone or other therapeutic options (options 1, 2, 3). Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Not applicable / Not stated / Unclear
Funding	Other (Funding was provided by Sparks)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING FENO AND SYMPTOMS + TREATMENT versus MONITORING SYMPTOMS + TREATMENT Protocol outcome 1: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment - Actual outcome for Children 5 -<16 : UHU - severe, requiring ≥8 hr hospital admission at 12 months; Group 1: 5/46, Group 2: 3/44; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Dose of regular asthma treatment (SABA, ICS) at End of Treatment - Actual outcome for Children 5 -<16 : Dose of regular therapy - final inhaled corticosteroid dose at 12 months; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; Exacerbation (need for OCS) at End of treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Lung Function at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Table 139: Powell 2011[1374]

Study	Powell 2011[1374]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=220)
Countries and setting	Conducted in Australia; Setting: Antenatal clinics
Line of therapy	Mixed line
Duration of study	Intervention time: Patients reviewed monthly until delivery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Doctor's diagnosis of asthma and were using inhaled therapy for asthma within the past year
Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Non-smoking pregnant women (aged >18 years) with asthma attending the antenatal clinics were recruited between weeks 12 and 20 of gestation. Women had a doctor's diagnosis of asthma and were using inhaled therapy for asthma within the past year. The diagnosis was confirmed by a respiratory physician's diagnostic interview.
Exclusion criteria	None specified
Recruitment/selection of patients	Recruited through antenal clinics, between weeks 12 and 20 of gestation
Age, gender and ethnicity	Age - Other: Mean age (95% CI): control: 28.8 (27.72 - 29.84); intervention: 28.1 (27.12 - 29.09). Gender (M:F): All female sample. Ethnicity: Australian born - control: 94/103 (91.3%); intervention: 96/103 (93.2%)
Further population details	
Indirectness of population	No indirectness
Interventions	(n=111) Intervention 1: Monitoring FeNO + treatment. The FeNO algorithm used a sequential process: first, the FeNO concentration was used to adjust the dose of inhaled corticosteroids; and second the ACQ score was used to adjust the dose of long acting β2 agonist. The cut-off points used for the dose reduction was 16 ppb, which was the upper 95% confidence limit of the mean FeNO concentration in pregnant women with asthma that remained controlled (ACQ <1.5) throughout pregnancy. The cut-off point for dose increase was 29 ppb. In terms of FeNO algorithm steps: steroid-naïve patients who needed inhaled corticosteroids started with budesonide 100mg twice per day. If a participant had undergone two dose increasements but the FeNO concentration remained greater than 29 ppb, the inhaled corticosteroid was not increased further. If such a participant was symptomatic (ACQ score >1.5), formoterol 6mg twice per day was added. When FeNO concentrations were between 16 ppb and 29 ppb, the inhaled corticosteroid dose was not changed. Symptomatic patients (ACQ score >1.5) with FeNO in the range 16-29 ppb were treated with an increase in the β2 agonist step, either with the addition of formoterol 6mg twice per day or an increase in formoterold dose. When FeNO concentrations were less than 16 ppb, inhaled corticosteroid dose was

	reduced by 50%. If participants were simultaneously symptomatic, formoterol 6mg per day was added. For participants taking formoterol, the budesonide dose was not reduced to zero, but to 100mg twice per day. Participants who remained uncontrolled and were taking the maximum dose step, were assessed with subsequent treatment decided by the respiratory physician. . Duration 4-6 months. Concurrent medication/care: At visit 1 (baseline characterisation), FeNO and spirometry were measured, and the asthma control questionnaire was administered. Asthma self-management skills were assessed and optimised. Eligible women commended a 2-week run-in period. Women using inhaled corticosteroids continued with their current dose, delivered as budesonide turbuhaler, with dose equivalence determined from guidelines. Women with uncontrolled asthma who were not using maintenance inhaled corticosteroids (n=31) were started on budesonide (200mg twice per day). At randomisatin (visit 2), measurements included asthma symptoms, FeNO, spirometry, ACQ score, and quality-of-life questionnaires. Women were reviewed monthly at the antenatal clinic until delivery. The research assistant collected data and treatment were sent by facsimile to the algorithm keeper. This person applied the relevant algorithm and sent the treatment recommendation to the research assistant in the clinic, who informed the participant. Participants were seen by the investigator in the antennal clinic if their asthma was uncontrolled and they were at the maximum treatment level of the algorithm. Telephone assessments were done 2 weeks after each clinic visit to assess symptoms and to encourage drug adherence. Further details: 1. Additional education training : Not applicable / Not stated / Unclear 2. Aim of intervention: Not applicable / Not stated / Unclear (n=109) Intervention 2: No FeNO monitoring + treatment - Monitoring symptoms + treatment. The clinical algorithm was based on asthma control, which was assessed with the Juniper ACQ with cut-off points defined as: well controlled (ACQ score <0.75), partially controlled (0.75-1.50), and uncontrolled (>1.5). After assessment of asthma control, a woman with uncontrolled asthma had her dose increased by one treatment step. Those with well controlled asthma had their inhaled corticosteroid dose reduced by one treatment step. The intermediate group represents partial loss of control, and no definite treatment change was undertaken. Participants who remained uncontrolled and were taking the maximum allowed dose were assessed and their subsequent treatment decided by the respiratory physician. . Duration 4-6 months. Concurrent medication/care: At visit 1 (baseline characterisation), FeNO and spirometry were measured, and the asthma control questionnaire was administered. Asthma self-management skills were assessed and optimised. Eligible women commended a 2-week run-in period. Women using inhaled corticosteroids continued with their current dose, delivered as budesonide turbuhaler, with dose equivalence determined from guidelines. Women with uncontrolled asthma who were not using maintenance inhaled corticosteroids (n=31) were started on budesonide (200mg twice per day). At randomisatin (visit 2), measurements included asthma symptoms, FeNO, spirometry, ACQ score, and quality-of-life questionnaires. Women were reviewed monthly at the antenatal clinic until delivery. The research assistant collected data and treatment were sent by facsimile to the algorithm keeper. This person applied the relevant algorithm and sent the treatment recommendation to the research assistant in the clinic, who informed the participant. Participants were seen by the

	investigator in the antennal clinic if their asthma was uncontrolled and they were at the maximum treatment level of the algorithm. Telephone assessments were done 2 weeks after each clinic visit to assess symptoms and to encourage drug adherence. Further details: 1. Additional education training : Not applicable / Not stated / Unclear 2. Aim of intervention: Not applicable / Not stated / Unclear
Funding	Academic or government funding (National Health and Medical Research Councul of Australia)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING FENO + TREATMENT versus MONITORING SYMPTOMS + TREATMENT

Protocol outcome 1: Quality of life at End of treatment
- Actual outcome for Adults and young people (16 years and over): AQLO-M total score at 4-6 months; Other: AQLQ-M 0-10 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Exacerbation (need for OCS) at End of treatment
- Actual outcome for Adults and young people (16 years and over): Exacerbation - mixed at 4-6 months; Group 1: 28/111, Group 2: 45/109; Risk of bias: ; Indirectness of outcome: No indirectness

Protocol outcome 3: Asthma control questionnaires at End of Treatment
- Actual outcome for Adults and young people (16 years and over): ACQ (mean ACQ score at exacerbation) at 4-6 months; Group 1: mean 1.97 (SD 0.95); n=111, Group 2: mean 2.02 (SD 0.79); n=109; ACQ 0-6 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults and young people (16 years and over): ACQ (mean ACQ score at unscheduled doctor visits) at 4-6 months; Group 1: mean 2.03 (SD 0.76); n=111, Group 2: mean 2.01 (SD 0.97); n=109; ACQ 0-6 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults and young people (16 years and over): ACQ (overall) at 4-6 months; Group 1: mean 0.56 (SD 0.67); n=111, Group 2: mean 0.72 (SD 0.8); n=109; ACQ 0-6 Top=High is poor outcome; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Dose of regular asthma treatment (SABA, ICS) at End of Treatment
- Actual outcome for Adults and young people (16 years and over): Dose of regular asthma treatment - ICS at 4-6 months; Group 1: 200/111, Group 2: 0/109; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Adults and young people (16 years and over): Dose of regular asthma treatment - SABA at 4-6 months; Group 1: 1/111, Group 2: 0/109; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 5: Lung Function at End of Treatment
- Actual outcome for Adults and young people (16 years and over): FEV1 (L) at 4-6 months; Other: ; Risk of bias: Low; Indirectness of outcome: No indirectness

- Actual outcome for Adults and young people (16 years and over): FEV1 (%) at 4-6 months; Other: ; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 6: Symptom free days at End of Treatment - Actual outcome for Adults and young people (16 years and over): Sympton free days (past week) at 4-6 months; Group 1: 7/111, Group 2: 6/109; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Rescue medication at End of Treatment; Time of school/work at End of Treatment

Table 140: Shaw 2007[1558]

Study	Shaw 2007[1558]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=118)
Countries and setting	Conducted in United Kingdom; Setting: Secondary - visits took place at hospital
Line of therapy	Mixed line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Participants had a diagnosis of asthma recorded in their general practitioner's (GP) notes. Participants attended hospital for tests to characterise their asthma: exhaled nitric oxide levels measured at flow of 50 ml/second, FEV1, and forced vital capacity (FVC), methacholine challenge test to determine the concentration of methacholine required to provoke a 20% fall in FEV1, induced sputum analysis, and skin prick tests.
Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	GP diagnosis of asthma. Participants were eligible if they had received at least one prescription for any antiasthma medication in the last 12 months. Study was restricted to current non-smokers with a past smoking history of less than 10 packs-years.
Exclusion criteria	Participants were excluded if they were considered by their physician to be poorly compliant or had had a severe asthma exacerbation, requiring a course of prednisolone, within 4 weeks of study entry.
Recruitment/selection of patients	Recruited from primary care - all suitable participants on the registers (held in general practices around Leicester, UK) who responded to an invitation from their GP to be contacted by the research team were invited to participate in the study.
Age, gender and ethnicity	Age - Mean (range): Intervention group: 50 (20-75). Control group: 52 (24-81).. Gender (M:F): 54/64. Ethnicity: Not specified
Further population details	
Indirectness of population	No indirectness
Interventions	(n=58) Intervention 1: Monitoring FeNO + treatment - Monitoring FeNO and symptoms + treatment. At each visit, patients asthma control was determined using a validated Juniper asthma control questionnaire, which scores asthma control from 0 to 6; a score of greater than 1.57 was used to identify poorly controlled asthma. Assessment of asthma control was made per protocol by investigators who were unaware of the participants' randomisation status. In the

	FeNO group, treatment was adjusted following a set protocol according to both the FeNO and Juniper scores. If the FeNO was greater than 26 ppb, inhaled corticosteroid treatment was increased; if it was less than 16 ppb or less than 26 ppb on two consecutive occasions, treatment was decreased. Bronchodilator therapy was increased if symptoms were uncontrolled, despite a FeNO of less than 26 ppb. *Hierarchy of Anti-Inflammatory Treatment: 1) Low dose inhaled steroid (100-200µg BDP bd). 2) Moderate dose inhaled steroid (200-800µg BDP bd). 3) High dose inhaled steroid (800-2000µg BDP bd). 4) High dose inhaled steroid (800-2000µg BDP bd) plus leukotriene antagonist. 5) Higher dose inhaled steroid (2000µg BDP bd) plus leukotriene antagonist. 6) Higher dose inhaled steroid (2000µg BDP bd) plus leukotriene antagonist plus oral Prednisolone 30mg. 2/52, then titrating dose reducing by 5mg/week **Hierarchy of Bronchodilator Treatment: 1) PRN short acting β2-agonists. 2) Long acting β2 agonist. 3) Long acting β2 agonist plus theophylline. 4) Long acting β2-agonist plus theophylline plus nebulised bronchodilator.. Duration 12 months. Concurrent medication/care: Participants were seen 2 weeks following characterisation of their asthma, and then every month for 4 months; they were seen every 2 months for a further 8 months. Each visit occurred at the same time of day and consisted of assessment of exhaled nitric oxide, spirometry, and post-bronchodilator FEV1, 20 minutes after 400 mcg albuterol at the end of every visit. Peak flow and symptom diaries were analysed and compliance assessed by monitoring adherence to prescription script collection. Participants were issued with self-management plans based on their baseline peak flow from the first 2 weeks of the study; if their peak flow fell to less than 70% of their best peak flow for 48 hours during the study, or their asthma deteriorated, they were asked to attend the hospital where they were assessed by a physician. Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Aim to decrease ICS in controlled patients (n=60) Intervention 2: No FeNO monitoring + treatment - Monitoring symptom control questionnaires + treatment. At each visit, patients asthma control was determined using a validated Juniper asthma control questionnaire, which scores asthma control from 0 to 6; a score of greater than 1.57 was used to identify poorly controlled asthma. Assessment of asthma control was made per protocol by investigators who were unaware of the participants' randomisation status. In the control group, treatment was doubled if the score was more than 1.57, and treatment was halved if the score was less than 1.57 for 2 consecutive months. Step 1: SABA as required. Step 2: Add inhaled steroid 200 to 800mcg/day BDP equivalent. Step 3: Add inhaled LABA. Step 4: Increase ICS up to 2000mcg/day and addition of 4th drug, e.g. LTRA, theophylline, LABA. Step 5: Oral prednisolone, high does ICS, refer to specialist care.. Duration 12 months. Concurrent medication/care: Participants were seen 2 weeks following characterisation of their asthma, and then every month for 4 months; they were seen every 2 months for a further 8 months. Each visit occurred at the same time of day and consisted of assessment of exhaled nitric oxide, spirometry, and post-bronchodilator FEV1, 20 minutes after 400 mcg albuterol at the end of every visit. Peak flow and symptom diaries were analysed and compliance assessed by monitoring adherence to prescription script collection. Participants were issued with self-management plans based on their baseline peak flow from the first 2 weeks of the study; if their peak flow fell to less than 70% of their best peak flow for 48 hours during the study, or their asthma deteriorated, they

	were asked to attend the hospital where they were assessed by a physician. Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Aim to decrease ICS in controlled patients
Funding	Academic or government funding (Trial supported by a grant from Asthma UK. Conflict of interest statement: authors received grants (research and travel) from Glaxo SmithKline and lecture fees from Astra eneca.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING FENO AND SYMPTOMS + TREATMENT versus MONITORING SYMPTOM CONTROL QUESTIONNAIRES + TREATMENT Protocol outcome 1: Exacerbation (need for OCS) at End of treatment - Actual outcome for Adults and young people (16 years and over): Exacerbation - course of oral steroids or antibiotics at 12 months; Group 1: 12/58, Group 2: 19/60; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Dose of regular asthma treatment (SABA, ICS) at End of Treatment - Actual outcome for Adults and young people (16 years and over): Dose of regular therapy - ICS, expressed as equivalent dose to BDP at 12 months; MD -338 (95%CI -640 to -37); Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Lung Function at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Table 141: Smith 2005[1611]

Study	Smith 2005[1611]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=110)
Countries and setting	Conducted in New Zealand; Setting: Primary care
Line of therapy	Unclear
Duration of study	Intervention time: Phase 1 stabilisation on optimum therapy (mean 22 and 25 weeks in the 2 groups); phase 2 dose adjustment using FeNO or control: 12 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Chronic asthma
Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	12 to 75 years of age with chronic asthma, managed in primary care, regular inhaled corticosteroids for six months or more with no change in dose in last 6 weeks
Exclusion criteria	Four or more courses of oral prednisone in the previous 12 months; admission to the hospital because of asthma in the previous 6 months or to the intensive care unit because of asthma at any time in the past; and cigarette smoking, either current or past, with a history of more than 10 pack-years.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (range): 44.8 (12 to 73) years. Gender (M:F): 41:69. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	(n=48) Intervention 1: Monitoring FeNO + treatment. Dose adjustment based on FeNO. Visits every 2 months for 1 year. Cut-off 15ppb (at an exhaled flow rate of 250 ml per second), above which an increase in the dose of inhaled corticosteroid was prescribed; this FeNO value is equivalent to 35 ppb at a flow rate of 50 ml per second. Subjects in the FeNO group had a predetermined “safety buffer” by which an upward (one-step) adjustment in the dose was provided to deal with deteriorating asthma in the absence of a rise in measured FeNO. Duration 12 months. Concurrent medication/care: 5 patients on LABA. Two-week run-in period. At the second visit, all patients were started on inhaled fluticasone. During phase 1, the dose of inhaled fluticasone was titrated downward in a stepwise manner until the optimal dose was deemed to have been achieved. Subjects received 750 µg per day to start (or 500 µg per day if their inhaled-corticosteroid requirement before enrolment was less than 200 µg per day of fluticasone or the equivalent).

	Further details: 1. Additional education training : Not applicable / Not stated / Unclear 2. Aim of intervention: Aim to increase ICS in uncontrolled patients (n=49) Intervention 2: No FeNO monitoring + treatment - Monitoring symptoms, BD use and lung function + treatment. Dose adjustments were based on predetermined thresholds in regard to symptoms, bronchodilator use, diurnal peak flows, and spirometry with an algorithm based on Global Initiative for Asthma 2002 criteria. Visits every 2 months for 1 year.. Duration 12 months. Concurrent medication/care: 8 patients on LABA. Two-week run-in period. At the second visit, all patients were started on inhaled. During phase 1, the dose of inhaled fluticasone was titrated downward in a stepwise manner until the optimal dose was deemed to have been achieved. Subjects received 750 µg per day to start (or 500 µg per day if their inhaled-corticosteroid requirement before enrolment was less than 200 µg per day of fluticasone or the equivalent). Further details: 1. Additional education training : Not applicable / Not stated / Unclear 2. Aim of intervention: Aim to increase ICS in uncontrolled patients
Funding	Academic or government funding (Otago Medical Research Foundation, Dunedin School of Medicine, University of Otago)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING FENO + TREATMENT versus MONITORING SYMPTOMS AND LUNG FUNCTION + TREATMENT

Protocol outcome 1: Exacerbation (need for OCS) at End of treatment
- Actual outcome for Adults and young people (16 years and over): Number of patients requiring at least one course of OCS at 12 months; Group 1: 13/46, Group 2: 15/48; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Rescue medication at End of Treatment
- Actual outcome for Adults and young people (16 years and over): Bronchodilator mean puffs/day (past 7 days) at 12 months; Group 1: mean 0.4 puffs/day (SD 1.04); n=46, Group 2: mean 0.4 puffs/day (SD 0.88); n=48; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Dose of regular asthma treatment (SABA, ICS) at End of Treatment
- Actual outcome for Adults and young people (16 years and over): Dose of fluticasone at 12 months; Group 1: mean 370 microg/day (SD 370); n=46, Group 2: mean 641 microg/day (SD 407); n=48; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Lung Function at End of Treatment
- Actual outcome for Adults and young people (16 years and over): FEV1 % predicted at 12 months; MD 3.8 (SE 4.4); Risk of bias: High; Indirectness of outcome: No indirectness

- Actual outcome for Adults and young people (16 years and over): PEF am (mean previous 7 days) at 12 months; MD 1.0 (SE 13.2); Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: Symptom free days at End of Treatment - Actual outcome for Adults and young people (16 years and over): Percentage of symptom-free days at 12 months; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Time of school/work at End of Treatment

Table 142: Syk 2013[1692]

Study	Syk 2013[1692]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=181)
Countries and setting	Conducted in Sweden; Setting: Primary care.
Line of therapy	Mixed line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Physician's diagnosis of asthma, had been on prescribed ICS treatment for at least 6 months, and had confirmed IgE sensitisation to at least 1 major airborne perennial allergen (dog, cat, or mite).
Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Eligible participants had a physician's diagnosis of asthma, had been on prescribed ICS treatment for at least 6 months, and had confirmed IgE sensitisation to at least 1 major airborne perennial allergen (dog, cat, or mite). In addition: age 18-64 years old, non-smokers since at least 1 year earlier and with a smoking history of <10 packs years.
Exclusion criteria	Not stated
Recruitment/selection of patients	Participants recruited from 17 primary health care centres in 7 different autonomous health care regions in central and southern Sweden.
Age, gender and ethnicity	Age - Mean (SD): 41 (12.4). Gender (M:F): 94/87. Ethnicity: Not stated

Further population details	
Indirectness of population	No indirectness
Interventions	(n=93) Intervention 1: Monitoring FeNO + treatment. In the FeNO-guided group, the anti-inflammatory treatment (ICS and leukotriene receptor antagonist [LTRA]) was adjusted according to an algorithm based on exhaled NO levels (FeNO <19ppb (men), <21ppb (women) - decrease one step; FeNO 19-23 (men), 21-25 (women) - no change; FeNO ≥24ppb (men), ≥26ppb (women) - increase one step (no change in treatment step if on step 4 or 5 and using ≤i2 inhalations of short-acting beta2 agonist per week); FeNO ≥30ppb (men), ≥32ppb (women)- increase two steps (only if one treatment step 1); grey zone of 5ppb applied to avoid frequent dose changes) and 6 fixed treatment steps (Steps 1-6: Budesonide (mcg/day): 0, 200, 400, 800, 800+LTRA, 1600+LTRA; Fluticasone (mcg/day): 0, 100, 250, 500, 500+LTRA; 1000+LTRA; Mometasone (mcg/day): 0, 100, 200, 400, 400+LTRA, 800+LTRA).. Duration 12 months. Concurrent medication/care: Capillary blood was sampled to confirm perennial allergy by using ImmunoCAP Rapid Wheeze/Rhinitis Child. All participants currently being treated with combination inhalers (corticosteroid plus LABA) were required to switch to the corresponding single corticosteroid inhaler to withdraw the LABA component. All patients switched SABA to a salbutamol inhaler which incorporates a dose counter. Venous blood was sampled for serum IgE All participants received a logbook to take home, in which they noted contacts with health care, changes in drug therapy, sick leave, or other problems between scheduled visits. Further details: 1. Additional education training : Not applicable / Not stated / Unclear 2. Aim of intervention: Aim to decrease ICS in controlled patients (The goal of the asthma treatment was to achieve and maintain clinical control, which implies that the patients should be free from symptoms; maintain normal activity levels, including physical exercise; maintain pulmonary function as close to normal as possible; avoid adverse effects of asthma medication; and have little or no need for reliever medication, all according to the Swedish Medical Product Agency recommendations.). (n=88) Intervention 2: No FeNO monitoring + treatment - Monitoring symptoms, BD use and lung function + treatment. In the control group, FeNO measurement was done but blinded to both operator and patient, and treatment was adjusted according to usual care, that is, based on patient-reported symptoms, SABA use, physical examination, and results of pulmonary function tests. In the control group, only the treatment steps (as described for the intervention group) were allowed, but changes in treatment steps were entirely at the discretion of the treating physician, and immediate changes over several steps were allowed. Permissible treatment steps (as described for the intervention group) basically followed the prevailing national guidelines at the time of the study start, issued in 2002 by the Swedish Medical Product Agency, with the exception that only LTRA was used as an add-on treatment.. Duration 12 months. Concurrent medication/care: Capillary blood was sampled to confirm perennial allergy by using ImmunoCAP Rapid Wheeze/Rhinitis Child. All participants currently being treated with combination inhalers (corticosteroid plus LABA) were required to switch to the corresponding single corticosteroid inhaler to withdraw the LABA component. All patients switched SABA to a salbutamol inhaler which incorporates a dose counter. Venous

	blood was sampled for serum IgE analysis. All participants received a logbook to take home, in which they noted contacts with health care, changes in drug therapy, sick leave, or other problems between scheduled visits. Further details: 1. Additional education training : Not applicable / Not stated / Unclear 2. Aim of intervention: Aim to decrease ICS in controlled patients (The goal of the asthma treatment was to achieve and maintain clinical control, which implies that the patients should be free from symptoms; maintain normal activity levels, including physical exercise; maintain pulmonary function as close to normal as possible; avoid adverse effects of asthma medication; and have little or no need for reliever medication, all according to the Swedish Medical Product Agency recommendations.).
Funding	Academic or government funding (Study was funded by the Stockholm country council (PickUp), Centre for Allergy Research, Korlinska Institutet, and the Research Foundation of the Swedish Asthma and Allergy Association. Support also from Aerocine AB (NIOX MINO instruments), Phadia AB (ImmuncoCAP Rapid), Meda AB (Buventol Easyhaler), and MSD Sweden (small grant). Authors not conflicts of interest: grants from Aerocrine AB and Research Council for Working Life and Social Research; stock/stock options as employee and co-founder of Aerocine, etc.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING FENO + TREATMENT versus MONITORING SYMPTOMS AND LUNG FUNCTION + TREATMENT

Protocol outcome 1: Exacerbation (need for OCS) at End of treatment
- Actual outcome for Adults and young people (16 years and over): Exacerbation - severe (≥1 event, course of OCS) at 12 months; Group 1: 8/93, Group 2: 6/88; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Asthma control questionnaires at End of Treatment
- Actual outcome for Adults and young people (16 years and over): ACQ - clinically important improvement (≥0.5) at 12 months; Group 1: 29/81, Group 2: 19/74; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: Rescue medication at End of Treatment
- Actual outcome for Adults and young people (16 years and over): Rescue medication (SABA use per week, at 8-12 months, i.e. ≥6 months) at 12 months; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 4: Dose of regular asthma treatment (SABA, ICS) at End of Treatment
- Actual outcome for Adults and young people (16 years and over): Dose of regular therapy (Budesonide equivalent dose) at 12 months; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 5: Lung Function at End of Treatment

- Actual outcome for Adults and young people (16 years and over): Lung function - FEV1 (litres) at 12 months; Group 1: mean -0.034 litres (SD 0.28); n=88, Group 2: mean -0.006 litres (SD 0.28); n=78; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Table 143: Szefler 2008[1693]

Study	Szefler 2008[1693]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=546)
Countries and setting	Conducted in USA; Setting: 10 centres
Line of therapy	Unclear
Duration of study	Intervention time: 46 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Physician diagnosis
Stratum	Children 5 -<16
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 12 to 20 years, with asthma; residents of urban census tracts in which at least 20 percent of households had incomes below the federal poverty threshold. Individuals receiving long-term control therapy were required to have symptoms of persistent asthma or evidence of uncontrolled disease. Individuals not receiving long-term control therapy were required to have both symptoms of persistent asthma and evidence of uncontrolled disease defined by NAEPP guidelines
Exclusion criteria	Excluded after the run-in if controller adherence was <25%. Participants with a urinary cotinine >100 excluded (active smokers)
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 14.4 ± 2.1 years in each group. Gender (M:F): 288:258. Ethnicity: Black: 347/546 (64%); Hispanic: 125/546 (23%); other/mixed: 74/546 (13%)
Further population details	
Indirectness of population	No indirectness
Interventions	(n=276) Intervention 1: Monitoring FeNO, lung function, BD use and symptoms + treatment. Exhaled nitric oxide

	(eNO) added to guideline-based care. FENO was measured for each participant at every visit, but only influenced treatment of the FENO Group. Control level and FENO data were entered into a computer program which generated two treatment options for the blinded physician, one for the Reference Group and another for the FENO Group. The treatment options were derived from protocol-defined treatment steps. Duration 46 weeks. Concurrent medication/care: For safety reasons, FENO was not allowed to increase treatment on the third consecutive visit without elevated symptoms. Also low FENO alone was not allowed to reduce therapy without a corresponding reduction in symptoms. Further details: 1. Additional education training : Not applicable / Not stated / Unclear 2. Aim of intervention: Aim to increase ICS in uncontrolled patients (n=270) Intervention 2: No FeNO monitoring + treatment - Monitoring symptoms, BD use and lung function + treatment. Based on National Asthma Education and Prevention Program (NAEPP) guidelines. Duration 46 weeks. Concurrent medication/care: Not stated Further details: 1. Additional education training : Not applicable / Not stated / Unclear 2. Aim of intervention: Aim to increase ICS in uncontrolled patients
Funding	Academic or government funding (National Institute of Allergy and Infectious Diseases, National Institutes of Health and National Centre for Research Resources, National Institutes of Health)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING FENO + TREATMENT versus MONITORING SYMPTOMS AND LUNG FUNCTION + TREATMENT

Protocol outcome 1: Exacerbation (need for OCS) at End of treatment
- Actual outcome for Children 5 -<16 : OCS at 46 weeks; Group 1: 89/250, Group 2: 113/244; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment
- Actual outcome for Children 5 -<16 : Hospitalisation at 46 weeks; Group 1: 9/250, Group 2: 11/244; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Children 5 -<16 : Unscheduled visits at 46 weeks; Group 1: 59/250, Group 2: 61/244; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Asthma control questionnaires at End of Treatment
- Actual outcome for Children 5 -<16 : Poor control at >20% of visits at 46 weeks; Group 1: 59/267, Group 2: 63/267; Risk of bias: Low; Indirectness of outcome: No indirectness
- Actual outcome for Children 5 -<16 : Asthma Control Test score in last month at 46 weeks; Group 1: mean 21.89 Not stated (SD 1.9); n=250, Group 2: mean 21.83 Not stated (SD 1.87); n=244; Asthma Control Test Not stated Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Dose of regular asthma treatment (SABA, ICS) at End of Treatment - Actual outcome for Children 5 -<16 : ICS daily dose (fluticasone) at 46 weeks; MD 118.9 (95%CI 48.5 to 189.3); Risk of bias: Low; Indirectness of outcome: Serious indirectness Protocol outcome 5: Lung Function at End of Treatment - Actual outcome for Children 5 -<16 : FEV1 % pred at 46 weeks; MD 0.8 (95%CI -0.51 to 2.07); Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 6: Symptom free days at End of Treatment - Actual outcome for Children 5 -<16 : Number of symptom-days in last 2 weeks at 46 weeks; Group 1: mean 1.93 days (SD 1.42); n=250, Group 2: mean 1.89 days (SD 1.41); n=244; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 7: Time of school/work at End of Treatment - Actual outcome for Children 5 -<16 : School days missed in last 2 weeks at 46 weeks; Group 1: mean 0.19 days (SD 0.47); n=250, Group 2: mean 0.23 days (SD 0.47); n=244; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; Rescue medication at End of Treatment

Table 144: Verini 2010[1836]

Study	Verini 2010[1836]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=64)
Countries and setting	Conducted in Italy; Setting: Secondary care
Line of therapy	Unclear
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis was made by a paediatric respiratory physician on the basis of clinical history of repeated episodes of coughing, dyspnoea, and wheezing, according to ATS-ERS criteria
Stratum	Children 5 -<16
Subgroup analysis within study	Not applicable
Inclusion criteria	Children with allergic asthma; age 6-17 years; referred to the Allergological and Pneumological Unity of the Paediatric Department, University of Chieti, Italy, between January 2005 and January 2006.
Exclusion criteria	Not stated

Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): FeNO group: 10.7 ± 2.4 years; GINA group: 11.3 ± 2.1 years, range 6-17 years. Gender (M:F): 36:28. Ethnicity: Caucasian
Further population details	
Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: Monitoring FeNO + treatment. Therapy was based on symptoms, short acting β2-agonist use, and lung function and FeNO measurements. Duration 12 months. Concurrent medication/care: Not stated Further details: 1. Additional education training : 2. Aim of intervention: (n=32) Intervention 2: No FeNO monitoring + treatment - Monitoring symptoms and lung function + treatment. Therapy was based on symptoms, short acting β2-agonist use, and lung function. Duration 12 months. Concurrent meication/care: ot stated Further details:1. Additional education training : 2. Aim of intervention:
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING FENO + TREATMENT versus MONITORING SYMPTOMS AND LUNG FUNCTION + TREATMENT

Protocol outcome 1: Rescue medication at End of Treatment
- Actual outcome for Children 5 -<16 : Number of patients with exacerbations (defined as the number of episodes of coughing, dyspnoea, and wheezing, according to ATS-ERS criteria, requiring short-acting β2-adrenergic agonist) at 12 months; Group 1: 16/32, Group 2: 26/32; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Dose of regular asthma treatment (SABA, ICS) at End of Treatment
- Actual outcome fo Children 5 -<16 : Number of patients not using inhaled corticosteroids or anti-leukotrienes at 12 months; Group 1: 2/32, Group 2: 6/32; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; Exacerbation (need for OCS) at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Lung Function at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

G.18 Challenge tests to monitor asthma control

Table 145: Koenig 2008[885]

Study	Koenig 2008[885]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=466)
Countries and setting	Conducted in Latvia, Multiple countries, USA; Setting: 50 sites in the US, three sites in Latin American, and two sites in Latvia.
Line of therapy	Mixed line
Duration of study	Intervention time: 40 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Either historical documentation of reversible airways disease within the last 24 months or an increase in FEV1 of at least 12% within 30 min of inhalation of 2 puffs (180 mcg) of albuterol.
Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Male and female patients, 12 years of age and older; asthma for at least 3 months and had been treated during the previous month with short-acting beta2-agonists, anticholinergics, or ICS (p250 mcg daily of fluticasone propionate (FP) or equivalent). At the screening visit, all patients were required to have a forced expiratory volume in 1 s (FEV1) between 60% and 95% of predicted normal
Exclusion criteria	Pregnancy; lifethreatening asthma, hospitalization attributable to asthma within the last 6 months, current smoker or a >10 pack-year history of smoking, a recent (within 2 weeks) upper or lower respiratory tract infection, or significant concurrent diseases. Medications that could confound the evaluation of the study treatments or treatment strategies were prohibited before and throughout the study, including inhaled (up to 250 mcg FP allowed prior to randomization), oral, or parenteral corticosteroids (with the exception of protocol defined use of oral corticosteroids following second consecutive assignment to the highest dose of FP), theophylline or other bronchodilators, leukotriene modifiers, anticholinergics, cromolyn, and nedocromil
Recruitment/selection of patients	Patients underwent physical examination, pulmonary function testing, and other pre-study procedures at the screening visit
Age, gender and ethnicity	Age - Mean (range): 34.8 (12–81), 34.8 (12–81) and 33.2 (12–72) years in the three groups. Gender (M:F): 85:115. Ethnicity: White FSCBHR 124 (79%), FPBHR 120 (77%), FPREF 124 (81%); Black FSCBHR 18 (12%), FPBHR 24 (15%), FPREF 16 (10%); Other FSCBHR 14 (9%), FPBHR 12 (8%), FPREF 14 (9%)

Further population details	
Indirectness of population	No indirectness
Interventions	(n=156) Intervention 1: Monitoring challenge tests + treatment - Monitoring direct challenge tests + treatment. Starting dose of treatment and adjustment of dose (at each 8 week visit for 40 weeks) based on severity class or BHR. Severity class included 4 treatment steps based on control over the past 14 days based on the highest of the following clinical measures (symptoms, BD use, PEFv, FEV1) or BHR. Treatment steps 1-no ICS (placebo); 2-FSC 100/50mcg BID; 3-FSC 250/50mcg BID; 4-500/50mcg BID. For BHR (methacholine PC20) severity class one >4mg/ml; two 1.1-4mg/ml; three 0.25-1mg/ml; four <0.25mg/ml.. Duration 40 weeks. Concurrent medication/care: SABA replaced by albuterol for study duration. ICS was fluticasone propionate using the DISKUS. If patient remained in step 4 for 2 or more visits they were given OCS. Further details: 1. Additional education training : Not applicable / Not stated / Unclear (n=154) Intervention 2: No challenge test monitoring + treatment - Monitoring symptoms, lung function and BD use + treatment. Starting dose of treatment and adjustment of dose (at each 8 week visit for 40 weeks) based on severity class (without BHR as a clinical measure). Severity class included 4 treatment steps based on control over the past 14 days based on the highest of the following clinical measures (symptoms, BD use, PEFv, FEV1). Treatment steps 1-no ICS (placebo); 2-FSC 100/50mcg BID; 3-FSC 250/50mcg BID; 4-500/50mcg BID. . Duration 40 weeks. Concurrent medication/care: SABA replaced by albuterol for study duration. ICS was fluticasone propionate using the DISKUS. If patient remained in step 4 for 2 or more visits they were given OCS. Further details: 1. Additional education training : Not applicable / Not stated / Unclear
Funding	Study funded by industry (GlaxoSmithKline, Research Triangle Park, NC.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING DIRECT CHALLENGE TESTS + TREATMENT versus MONITORING SYMPTOMS, LUNG FUNCTION AND BD USE + TREATMENT

Protocol outcome 1: Mortality at End of Treatment
- Actual outcome for Adults and young people (16 years and over): Death at 40 weeks; Group 1: 1/105, Group 2: 0/107; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Exacerbation (need for OCS) at End of treatment
- Actual outcome for Adults and young people (16 years and over): Asthma exacerbation (not defined) at 40 weeks; Group 1: 22/105, Group 2: 26/107; Risk of bias: Very high; Indirectness of outcome: Exacerbations not defined, serious indirectness.

Protocol outcome 3: Rescue medication at End of Treatment - Actual outcome for Adults and young people (16 years and over): Albuterol use (puff/day) at 40 weeks; Group 1: mean -0.8 puffs/day (SD 1.8); n=105, Group 2: mean -0.7 puffs/day (SD 1.8); n=107; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Dose of regular asthma treatment (SABA, ICS) at End of Treatment - Actual outcome for Adults and young people (16 years and over): Mean inhaled corticosteroid daily dose over treatment period (mcg) at 40 weeks; MD 131.2 (95%CI 83.2 to 178.5) (P=0.037 van Elteren tests); Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: Lung Function at End of Treatment - Actual outcome for Adults and young people (16 years and over): AM PEF at 40 weeks; Group 1: mean 16.9 L/min (SD 92.2); n=105, Group 2: mean 25.5 L/min (SD 92.1); n=107; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people (16 years and over): PM PEF at 40 weeks; Group 1: mean 16.4 L/min (SD 89.1); n=105, Group 2: mean 22.4 L/min (SD 88.9); n=107; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people (16 years and over): Pre-dose FEV1 at 40 weeks; Group 1: mean 0.06 L (SD 0.51); n=105, Group 2: mean 0.11 L (SD 0.52); n=107; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 6: Symptom free days at End of Treatment - Actual outcome for Adults and young people (16 years and over): % symptom-free days at 40 weeks; Group 1: mean 13 % (SD 56.2); n=105, Group 2: mean 18.1 % (SD 54.9); n=107; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Time of school/work at End of Treatment

Table 146: Lipworth 2012[1018]

Study	**STAMINA trial: Lipworth 2012[1018]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=157)
Countries and setting	Conducted in United Kingdom; Setting: Primary care
Line of therapy	Mixed line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: History of mild to moderate persistent asthma

Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Between 18 and 65 years of age and with a history of mild to moderate persistent asthma; prebronchodilator FEV 1 was required to be > 60% predicted for the purposes of challenge testing.
Exclusion criteria	Not stated
Recruitment/selection of patients	At the time of patients' entry into the study, AHR was established through a provocative dose of mannitol causing a 10% fall in FEV 1 (PD 10) ≤ 635 mg at the end of the step-down period. Patients initially underwent step-down of their existing treatment with follow-up every 2 weeks. Patients on combination inhalers were switched to an equivalent dose of the same ICS only. The dose of ICS was then halved every 2 weeks until patients were taking 200 m g/d beclomethasone dipropionate equivalent or they became clinically unstable. Once unstable, patients were stepped back up to the last stable dose of ICS. All patients were then converted to an equivalent dose of the reference ICS, namely ciclesonide, to be taken throughout the rest of the study.
Age, gender and ethnicity	Age - Mean (SD): Control 53.7 (1.7); intervention 53.2 (1.6) years. Gender (M:F): Not stated. Ethnicity: Not stated
Further population details	
Indirectness of population	Serious indirectness: Patients initially underwent step-down of their existing treatment. Patients on combination inhalers were switched to an equivalent dose of the same ICS only (unclear whether LABA was continued)
Interventions	(n=80) Intervention 1: Monitoring challenge tests + treatment - Monitoring indirect challenge tests + treatment. Treatment adjusted based on mannitol AHR only, every 2 months for 12 months. ICS dose increased by one step every 2 months until they became unresponsive to mannitol (PD10>635mg). Treatment steps: ciclesonide, step 1: 80mcg once daily, step 2: 160mcg once daily, step 3: 320mcg once daily, step 4: 160mcg and 320mcg BID, step 5: 320mcg BID.. Duration 12 months. Concurrent medication/care: Initial step-down of existing treatment and those on combination inhalers switched to same ICS only. Dose of ICS halved every 2 weeks until taking 200ug/d beclomethasone dipropionate or equivalent or became unstable - put back to last stable ICS dose. All then converted to equivalent ciclesonide. Further details: 1. Additional education training : Not applicable / Not stated / Unclear (n=77) Intervention 2: No challenge test monitoring + treatment - Monitoring symptoms, lung function and BD use + treatment. Treatment adjusted according to BTS guidelines every 2 months for 12 months. ICS dose increased by one step if 1. fall in PEF >20% baseline; 2. fall in FEV1 >20% baseline; 3. BD use more than 0.5puffs/day; 4. symptom score >0.5. Treatment steps: ciclesonide, step 1: 80mcg once daily, step 2: 160mcg once daily, step 3: 320mcg once daily, step 4: 160mcg and 320mcg BID, step 5: 320mcg BID.. Duration 12 months. Concurrent medication/care: Initial step-down of existing treatment and those on combination inhalers switched to same ICS only. Dose of ICS halved every 2 weeks until taking 200ug/d beclomethasone dipropionate or equivalent or became unstable - put back to last stable ICS dose. All

	then converted to equivalent ciclesonide. Further details: 1. Additional education training : Not applicable / Not stated / Unclear
Funding	Study funded by industry (University Departmental grants as well as by Pharmaxis, who supplied mannitol as a gift and donated an unrestricted educational grant. Nycomed supplied the ciclesonide inhalers as a gift and also provided an unrestricted educational grant.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING INDIRECT CHALLENGE TESTS + TREATMENT versus MONITORING SYMPTOMS, LUNG FUNCTION AND BD USE + TREATMENT

Protocol outcome 1: Quality of life at End of treatment
- Actual outcome for Adults and young people (16 years and over): mini AQLQ at 12 months; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Exacerbation (need for OCS) at End of treatment
- Actual outcome for Adults and young people (16 years and over): Severe exacerbations requiring oral corticosteroids at 12 months; Group 1: 12/61, Group 2: 13/58; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Rescue medication at End of Treatment
- Actual outcome for Adults and young people (16 years and over): Reliever use (puffs/day) at 12 months; MD 0.31 (95%CI -0.12 to 0.73) (P=0.16) (final value is lower in the intervention group, therefore mean difference analysed as -0.31); Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Dose of regular asthma treatment (SABA, ICS) at End of Treatment
- Actual outcome for Adults and young people (16 years and over): ciclesonide dose mcg at 12 months; MD 306 (95%CI 241.6 to 370.2); Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: Lung Function at End of Treatment
- Actual outcome for Adults and young people (16 years and over): AM PEF at 12 months; MD 1.5 (95%CI -37.7 to 34.7) (P=0.93); Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults and young people (16 years and over): FEV1% at 12 months; Group 1: mean 2 % (SD 22.3); n=61, Group 2: mean 1.7 % (SD 24.9); n=58; % 0-100 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults and young people (16 years and over): PEF% at 12 months; Group 1: mean 3.1 % (SD 25.9); n=61, Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Mortality at End of Treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of

	Treatment

Table 147: Nuijsink 2007[1248]

Study	**Children Asthma Therapy Optimal (CATO) Study trial: Nuijsink 2007[1248]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=210)
Countries and setting	Conducted in Netherlands; Setting: 15 centres; secondary care
Line of therapy	Mixed line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Documented clinical history of moderate persistent asthma, according to GINA guidelines.
Stratum	Children 5 -<16
Subgroup analysis within study	Not applicable
Inclusion criteria	Children with clinically stable asthma living in the Netherlands, aged 6–16 yrs and with a documented clinical history of moderate persistent asthma, according to GINA guidelines. All patients gave a positive, class ≥1, radioallergosorbent test result for one or more airborne allergens and used ≥200 µg/day fluticasone or an equivalent dose of other ICS. In children treated with 500 mg/day fluticasone who did not meet the criteria for randomisation after 1 month, the dose of ICS was tapered down to 200 mg/day fluticasone for a further 2 months before randomisation. After run-in, children were randomised into one of two treatment strategy arms if they showed a cumulative symptom score ≥14 during the last 2 weeks of the run-in period and/or a PD20<150mg.
Exclusion criteria	Not stated
Recruitment/selection of patients	Selected on the basis of symptom scores and/or the presence of airway hyper-responsiveness
Age, gender and ethnicity	Age - Mean (SD): Intervention: 10.8+/-2.4 years; control: 10.9+/-2.5 years. Gender (M:F): 117:89. Ethnicity: Not stated
Further population details	
Indirectness of population	Serious indirectness: Patients initially underwent step-down of their existing treatment.
Interventions	(n=102) Intervention 1: Monitoring challenge tests + treatment - Monitoring direct challenge tests + treatment. Treatment adjusted on the basis of AHR and symptom score according to a three step medication level algorithm. AHR methacholine dosimeter method PD20.- Increase by 1: PD20<100mcg and SS<14 or PD20<300mcg and SS>=14- No

	change: PD20 100-300mcg and SS<14 or PD20>=300mcg and SS>=14- Decrease by 1: PD20>300mcg and SS<14.. Duration 2 years. Concurrent medication/care: During run-in patients put on 100 or 250 FP BID depending on equivalent treatment before run-in. Further details: 1. Additional education training : Not applicable / Not stated / Unclear (n=104) Intervention 2: No challenge test monitoring + treatment - Monitoring symptoms + treatment. Treatment adjusted on the basis of symptom score only according to a three step medication level algorithm. Symptoms from diary 2 weeks before visit. - Increase by 1: SS>=14- No change: SS 0-14- Decrease by 1: SS=0. Duration 2 years. Concurrent medication/care: During run-in patients put on 100 or 250 FP BID depending on equivalent treatment before run-in. Further details: 1. Additional education training : Not applicable / Not stated / Unclear
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING DIRECT CHALLENGE TESTS + TREATMENT versus MONITORING SYMPTOMS + TREATMENT Protocol outcome 1: Exacerbation (need for OCS) at End of treatment - Actual outcome for Children 5 -<16 : At least one exacerbation at 2 years; Group 1: 16/102, Group 2: 17/104; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Dose of regular asthma treatment (SABA, ICS) at End of Treatment - Actual outcome for Children 5 -<16 : Mean daily ICS dose for treatment period at 2 years; Group 1: mean 562 mcg/day (SD 239); n=85, Group 2: mean 478 mcg/day (SD 256); n=90; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Lung Function at End of Treatment - Actual outcome for Children 5 -<16 : FEV1 % at 2 years; MD 6.0 (95%CI 1.2 to 10.8); Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Symptom free days at End of Treatment - Actual outcome for Children 5 -<16 : % symptom-free days (in last 3 months) at 2 years; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Time of school/work at End of Treatment

Table 148: Sont 1999[1625]

Study	AMPUL trial: Sont 1999[1625]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=75)
Countries and setting	Conducted in Netherlands; Setting: Secondary care
Line of therapy	Mixed line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: History of episodic chest tightness and wheezing in the previous year and visiting a chest physician for their asthma.
Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who were visiting a chest physician for their asthma at one of the outpatient clinics of four hospitals in the Leiden area; history of episodic chest tightness and wheezing in the previous year; AHR was established through a 20% decrease in FEV1 in response to a provocative concentration of inhaled methacholine (PC20) of < 8 mg/ml; nonsmokers at the time of recruitment (> 1 yr; < 5 pack-yr), and were atopic, between 18 and 50 yr of age, and had had a history of episodic chest tightness and wheezing in the previous year. Atopy was assessed through a positive skin-prick test (> 3 mm wheal) to one or more common airborne allergen extracts. Prebronchodilator FEV1 was more than 50% predicted and > 1.5 L, whereas postbronchodilator FEV1 was within the normal range (> 80% predicted). Subjects were eligible when they had used no other medication than regular inhaled steroids and/or beta-agonists as needed for their asthma during the 6 mo before entry. All subjects gave their written informed consent
Exclusion criteria	Not stated
Recruitment/selection of patients	Outpatient clinics of four hospitals in the Leiden area
Age, gender and ethnicity	Age - Mean (SD): Intervention 31.5 (1.7); control 28.2 (1.3) years. Gender (M:F): 37:38. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	(n=34) Intervention 1: Monitoring challenge tests + treatment - Monitoring direct challenge tests + treatment. Treatment adjusted at each 3 month visit based on severity class or AHR. Severity class included 4 treatment steps based on the highest of the following clinical measures (symptoms, BD use, PEFv, FEV1 or BHR). Treatment steps 1-no ICS; 2-low dose ICS; 3-intermediate dose ICS; 4-hig dose ICS plus OCS course. For AHR (methacholine PC20) severity class one

	>4mg/ml; two 1.0-4mg/ml; three 0.25-1mg/ml; four <0.25mg/ml.. Duration 2 years. Concurrent medication/care: SABA used as needed Further details: 1. Additional education training : Not applicable / Not stated / Unclear (n=41) Intervention 2: No challenge test monitoring + treatment - Monitoring symptoms, lung function and BD use + treatment. Treatment adjusted at each 3 month visit based on severity class ONLY. Severity class included 4 treatment steps based on the highest of the following clinical measures (symptoms, BD use, PEFv, FEV1). Treatment steps 1-no ICS; 2-low dose ICS; 3-intermediate dose ICS; 4-hig dose ICS plus OCS course. . Duration 2 years. Concurrent medication/care: SABA use as needed Further details: 1. Additional education training : Not applicable / Not stated / Unclear
Funding	Academic or government funding (The Netherlands Asthma Foundation)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING DIRECT CHALLENGE TESTS + TREATMENT versus MONITORING SYMPTOMS, LUNG FUNCTION AND BD USE + TREATMENT Protocol outcome 1: Lung Function at End of Treatment - Actual outcome for Adults and young people (16 years and over): FEV1 L at 2 years; Group 1: mean 78 mL/year (SD 34); n=32, Group 2: mean -7 mL/year (SD 36); n=35; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; Exacerbation (need for OCS) at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

G.19 Monitoring adherence to treatment

Table 149: BURGESS 2010[246]

Study	**Burgess 2010[246]**
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=26)
Countries and setting	Conducted in Australia; Setting: Paediatric asthma clinic, outer metropolitan general hospital
Line of therapy	Mixed line
Duration of study	Intervention time: 4 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Dx with asthma
Stratum	Children 5 -<16 with uncontrolled asthma: Children 6-14 years, asthma not well controlled despite preventative medication ('unstable asthma')
Subgroup analysis within study	Not applicable:
Inclusion criteria	Aged 6-14 years; asthma not well controlled (based on a reported history of asthma symptoms occuring more than twice a week and requiring reliever medication and/or lung function FEV1 <80%)
Exclusion criteria	nr
Recruitment/selection of patients	nr
Age, gender and ethnicity	Age - Range: 6-14 years. Gender (M:F): 17/9. Ethnicity:
Further population details	1. Cognitive function: Not applicable / Not stated / Unclear 2. Disability: Not applicable / Not stated / Unclear 3. Near fatal asthma attacks: Not applicable / Not stated / Unclear 4. Social economic disadvantage: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=14) Intervention 1: Adherence monitoring + treatment - Adherence monitoring and feedback + treatment. Electronic monitoring device (Smartinhaler, Nexus 6; counts number of doses). Adherence calculated at each monthly review as a % of the number of prescribed doses registered by the smartinhaler. Adherence shared with child and carer and incorporated into the management plan (direct feedback from respiratory physician). Duration 4 months. Concurrent medication/care: In both groups: personalised asthma education and generic written information. Personalised asthma management plan devised, assessment of inhaler technique. Further details: 1. Additional education training : Additional education in both groups (n=12) Intervention 2: Usual care + treatment - Usual care (no adherence feedback) + treatment. Adherence remains unknown to physician. Duration 4 months. Concurrent medication/care: In both groups: personalised asthma education and generic written information. Personalised asthma management plan devised, assessment of inhaler technique. Further details: 1. Additional education training : Additional education in both groups

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ADHERENCE MONITORING AND FEEDBACK + TREATMENT versus USUAL CARE (NO ADHERENCE FEEDBACK) + TREATMENT Protocol outcome 1: Adherence at End of Treatment - Actual outcome for Children 5 -<16 with uncontrolled asthma: % of prescribed doses measured by the electronic inhaler at 4 months; Group 1: mean 84.2 % (SD 26.3); n=14, Group 2: mean 55.3 % (SD 26.3); n=12; % of prescribed doses measured by the electronic inhaler 0-100 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Exacerbation (need for OCS) at End of treatment - Actual outcome for Children 5 -<16 with uncontrolled asthma: Acute exacerbation at 4 months; Group 1: 3/14, Group 2: 1/12; Risk of bias: Very high; Indirectness of outcome: Serious indirectness Protocol outcome 3: Rescue medication at End of Treatment - Actual outcome for Children 5 -<16 with uncontrolled asthma: Reliever medication 3 or more times a week at 4 months; Group 1: 2/14, Group 2: 0/12; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Lung Function at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Table 150: ONYIRIMBA 2003[1270]

Study	Onyirimba 2003[1270]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in USA; Setting: hospital asthma centre
Line of therapy	Mixed line
Duration of study	Intervention time: 10 weeks
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Adults with moderate to severe asthma; referred to hospital asthma centre
Stratum	Adults and young people with uncontrolled asthma: Adults with moderate to severe asthma
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with moderate to severe asthma; referred to hospital asthma centre; low socioeconomic status; FEV1 <80% predicted and BDR of ≥15%; regular use of ICS (LABA, OCS and theophylline permissible); smokers not excluded.
Exclusion criteria	nr
Recruitment/selection of patients	nr
Age, gender and ethnicity	Age - Range: >18 years. Gender (M:F): 3/16. Ethnicity:
Further population details	1. Cognitive function: Not applicable / Not stated / Unclear 2. Disability: Not applicable / Not stated / Unclear 3. Near fatal asthma attacks: Not applicable / Not stated / Unclear 4. Social economic disadvantage: Low social economic status
Indirectness of population	Serious indirectness: Includes severe asthma
Interventions	(n=15) Intervention 1: Adherence monitoring + treatment - Adherence monitoring and feedback + treatment. Electronic monitoring device (MDI Chronologs and electronic recording of actuations for 10 weeks). Received direct feedback on ICS use from the clinician investigator and discussion of techniques to improve adherence (in addition to standard asthma care). Duration 10 weeks. Concurrent medication/care: In both groups: If necessary, ICS switched to a twice daily regime; 3 week intensive asthma education (four 30-60min sessions) by a nurse and/or respiratory therapist blinded to the patient group (goals of therapy, signs of worsening asthma, medications, importance of prophylactic medication, MDI technique and PEF). Physician input, therapy adjustment and implementation of a management plan based on PEF or symptoms at these sessions Further details: 1. Additional education training : Additional education in both groups

	(n=15) Intervention 2: Usual care + treatment - Usual care (no adherence feedback) + treatment. Adherence data not provided to physician. Standard asthma care only. Duration 10 weeks. Concurrent medication/care: In both groups: If necessary, ICS switched to a twice daily regime; 3 week intensive asthma education (four 30-60min sessions) by a nurse and/or respiratory therapist blinded to the patient group (goals of therapy, signs of worsoning asthma, medications, importance of prophylactic medication, MDI technique and PEF). Physician input, therapy adjustment and implementation of a management plan based on PEF or symptoms at these sessions Further details: 1. Additional education training : Additional education in both groups
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ADHERENCE MONITORING AND FEEDBACK + TREATMENT versus USUAL CARE (NO ADHERENCE FEEDBACK) + TREATMENT Protocol outcome 1: Quality of life at End of treatment - Actual outcome for Adults and young people with uncontrolled asthma: AQLQ at 10 weeks; Group 1: mean change score 1.13 (SD 0.31); n=10, Group 2: mean change score 0.76 (SD 0.33); n=9; AQLQ 1-7 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Lung Function at End of Treatment - Actual outcome for Adults and young people with uncontrolled asthma: FEV1 % at 10 weeks; Group 1: mean 0.04 L (SD 0.11); n=10, Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Adherence at End of Treatment; Mortality at End of Treatment; Exacerbation (need for OCS) at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Table 151: OTSUKI 2009[1279]

Study	**Otsuki 2009[1279]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=250)
Countries and setting	Conducted in USA; Setting: Community; recruited from paediatric ED
Line of therapy	Mixed line

Duration of study	Intervention time: 18 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Phys Dx asthma
Stratum	Children 5 -<16 with uncontrolled asthma: Children 2-12 years with asthma recruited from ED discharge records; 2 ED visits or 1 hospitalisation for asthma in previous year
Subgroup analysis within study	Not applicable
Inclusion criteria	Children with asthma recruited from ED discharge records; 2-12 years old; had Phys Dx asthma; 2 ED visits or 1 hospitalisation for asthma in previous year; prescribed an asthma controller medication)
Exclusion criteria	nr
Recruitment/selection of patients	2001-2003
Age, gender and ethnicity	Age - Range: 2-12 years. Gender (M:F): 106/61. Ethnicity:
Further population details	1. Cognitive function: Not applicable / Not stated / Unclear 2. Disability: Not applicable / Not stated / Unclear 3. Near fatal asthma attacks: Not applicable / Not stated / Unclear 4. Social economic disadvantage: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness: Mean age within 5-16 year age group
Interventions	(n=83) Intervention 1: Adherence monitoring + treatment - Adherence monitoring and feedback + treatment. Feedback of adherence (electronic medication monitors), goal-setting and reinforcement of adherence goals and strategies for self-monitoring of med use plus home-based education as in the control group. Duration 18 months. Concurrent medication/care: In both groups: Five 30min home visits by trained asthma educators Further details: 1. Additional education training : Additional education in both groups (n=84) Intervention 2: Usual care + treatment - Usual care (no adherence feedback) + treatment. Home-based asthma education programme alone (review of asthma regime; training in inhaler technique; development of asthma action plan and other education materials). Duration 18 months. Concurrent medication/care: In both groups: Five 30min home visits by trained asthma educators Further details: 1. Additional education training : Additional education in both groups
Funding	Academic or government funding (National Heart Lung and Blood Institute)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ADHERENCE MONITORING AND FEEDBACK + TREATMENT versus USUAL CARE (NO ADHERENCE FEEDBACK) + TREATMENT	

Protocol outcome 1: Adherence at End of Treatment - Actual outcome for Children 5 -<16 with uncontrolled asthma: % self-reported adherence in previous 6 months at 18 months; Group 1: mean 87.33 % (SD 25.24); n=76, Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children 5 -<16 with uncontrolled asthma: Number of canister refills (100% adherence = 3.0) at 18 months; Group 1: mean 0.58 (SD 0.86); n=76, Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Exacerbation (need for OCS) at End of treatment - Actual outcome for Children 5 -<16 with uncontrolled asthma: Courses of OCS in previous 6 months at 18 months; Group 1: mean 0.96 (SD 1.59); n=76, Risk of bias: High; Indirectness of outcome: Serious indirectness Protocol outcome 3: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment - Actual outcome for Children 5 -<16 with uncontrolled asthma: Hospitalisation in previous 6 months at 18 months; Group 1: mean 12 (SD 15.8); n=76, Risk of bias: High; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Lung Function at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Table 152: WILLIAMS 2010[1899]

Study	**Williams 2010[1899]**
Study type	RCT (Cluster randomised; Parallel)
Number of studies (number of participants)	1 (n=2698)
Countries and setting	Conducted in USA; Setting: Primary care
Line of therapy	Mixed line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: at least one physician Dx of asthma and no Dx of COPD or congestive heart failure
Stratum	Adults and young people overall: Age 5-56 years wtih ICS prescription
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 5-56 years; an electronic prescription for an ICS between Jan 2005 and April 2007; at least one physician Dx of asthma and no Dx of COPD or congestive heart failure; at least one visit to primary care provider in the previous year

Exclusion criteria	nr
Recruitment/selection of patients	August 2007 to July 2008
Age, gender and ethnicity	Age - Range: 5-56 years. Gender (M:F): Define. Ethnicity:
Further population details	1. Cognitive function: Not applicable / Not stated / Unclear 2. Disability: Not applicable / Not stated / Unclear 3. Near fatal asthma attacks: Not applicable / Not stated / Unclear 4. Social economic disadvantage: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness: Mean age within adult and young person age group
Interventions	(n=1335) Intervention 1: Adherence monitoring + treatment - Adherence monitoring and feedback + treatment. Physicians provided with adherence information (from refill data) when reviewing and writing prescriptions. Adherence calculated from prescription and refill data and uploaded onto the ePrescribing system every 2 weeks and could be viewed by physicians. General and detailed adherence information could be viewed. Physicians also received specific instructions on how to intepret the adherence data.. Duration 12 months. Concurrent medication/care: GP practices in both groups received information on the most recent asthma guidelines, and methods for discussing nonadherence with their patients. Further details: 1. Additional education training : No education in both groups (n=1363) Intervention 2: Usual care + treatment - Usual care (no adherence feedback) + treatment. GP used e Prescribing system but could not view asthma patient's adherence data.. Duration 12 months. Concurrent medication/care: GP practices in both groups received information on the most recent asthma guidelines, and methods for discussing nonadherence with their patients. Further details: 1. Additional education training : No education in both groups
Funding	Academic or government funding (Grants from National Heart Lung and Blood Institute, National Institute of Allergy and Infectious Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes for Health, Fund for Henry Ford Hospital, American Asthma Foundation.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ADHERENCE MONITORING AND FEEDBACK + TREATMENT versus USUAL CARE (NO ADHERENCE FEEDBACK) + TREATMENT

Protocol outcome 1: Adherence at End of Treatment
- Actual outcome for Adults and young people overall: % adherence to prescription refills in previous 3 months at 12 months; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Exacerbation (need for OCS) at End of treatment - Actual outcome for Adults and young people overall: OCS use at 12 months; HR 1.07 (95%CI 0.89 to 1.29) Reported; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people overall: OCS use at 12 months; RR Adjusted RR 1.11 (95%CI 0.92 to 1.34) (P=0.28 (negative binomial regression model)); Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 3: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment - Actual outcome for Adults and young people overall: Asthma-related Hospitalisation at 12 months; HR 0.86 (95%CI 0.32 to 2.29) Reported; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people overall: Asthma-related Hospitalisation at 12 months; RR Adjusted RR 0.87 (95%CI 0.33 to 2.29) (P=0.77 (negative binomial regression model)); Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people overall: Asthma-related ED visit at 12 months; HR 1.22 (95%CI 0.83 to 1.78) Reported; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people overall: Asthma-related ED visit at 12 months; RR Adjusted RR 1.12 (95%CI 0.74 to 1.69) (P=0.60 (negative binomial regression model)); Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Lung Function at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

G.20 Monitoring inhaler technique

Study	Al-showair 2007[29]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=71)
Countries and setting	Conducted in United Kingdom; Setting: Secondary care - patients attending an outpatient clinic
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 6 weeks
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Patients with asthma attending an outpatient clinic and receiving ICS
Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with asthma attending an outpatient clinic; receiving ICS from an MDI without a spacer; identified with poor inhaler technique (good coordination but inhaled too fast IFR ≥90l/min).
Exclusion criteria	Experienced an acute exacerbation of asthma within 4 weeks prior to recruitment; hearing problems and/or unable to distinguish between one and two tones produced by the 2TT tool; patients who started to inhale before actuating a dose (poor coordination).
Recruitment/selection of patients	nr
Age, gender and ethnicity	Age - Mean (SD): Verbal group 52.6 (15.7); Verbal+2TT group 58.3 (13.7). Gender (M:F): 27/44. Ethnicity:
Further population details	1. Cognitive function: Not applicable / Not stated / Unclear 2. Disability: Not applicable / Not stated / Unclear 3. Social economic disadvantage: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=36) Intervention 1: Monitoring inhaler technique + feedback - Monitoring using electronic devices + feedback. Verbal training on the most desirable inhalation technique with emphasis on breathing out slowly as far as comfortable and actuating a dose at or soon after the start of a slow inhalation. Also trained on how to use the 2Tone Trainer every morning and night to obtain the one-tone sound and to use the same inhalation procedure when using their MDI.. Duration 6 weeks. Concurrent medication/care: nr Further details: 1. Additional education training : Additional education in both groups (Counselled on compliance with the prescribed medication).

	(n=36) Intervention 2: Monitoring inhaler technique + feedback - Visual monitoring + feedback. Verbal training on the most desirable inhalation technique with emphasis on breathing out slowly as far as comfortable and actuating a dose at or soon after the start of a slow inhalation.. Duration 1 visit (6 weeks follow-up). Concurrent medication/care: nr Further details: 1. Additional education training : Additional education in both groups (Counselled on compliance with the prescribed medication).
Funding	Other (2 Tone trainers donated by Canday Medical Ltd.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VERBAL TRAINING PLUS ELECTRONIC DEVICE TO PRACTICE versus VERBAL TRAINING

Protocol outcome 1: Quality of life at End of treatment
- Actual outcome for Adults and young people (16 years and over): mini AQLQ at 6 weeks; Group 1: mean 4.6 (SD 1); n=36, Group 2: mean 4.2 (SD 1); n=35; mini AQLQ 1-7 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung Function at End of Treatment
- Actual outcome for Adults and young people (16 years and over): FEV1 L at 6 weeks; Group 1: mean 1.93 L (SD 0.63); n=36, Group 2: mean 2.16 L (SD 0.74); n=35; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Mortality at End of Treatment; Exacerbation (need for OCS) at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Study	Ammari 2013-1[43]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=34)
Countries and setting	Conducted in United Kingdom; Setting: Primary care
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 6 weeks
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Patients with asthma who collected their MDI prescriptions from community pharmacies
Stratum	Adults and young people (16 years and over):
Subgroup analysis within study	Stratified then randomised: Adults and children
Inclusion criteria	Aged 4-45 years; prescribed at least one MDI without a spacer device including a preventer; identified with poor inhaler technique (defined as poor hand-lung coordination and an IFR ≥90l/min).
Exclusion criteria	Experienced an acute exacerbation of asthma or received OCS within 4 weeks prior to recruitment; had other illnesses adversely affecting their respiratory system; hearing problems and/or unable to distinguish between one and two tones produced by the 2TT tool.
Recruitment/selection of patients	nr
Age, gender and ethnicity	Age - Mean (SD): 40.7 (9.7). Gender (M:F): 11/23. Ethnicity:
Further population details	1. Cognitive function: Not applicable / Not stated / Unclear 2. Disability: Not applicable / Not stated / Unclear 3. Social economic disadvantage: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=17) Intervention 1: Monitoring inhaler technique + feedback - Monitoring using electronic devices + feedback. All patients selected due to a fast inhalation (most common inhaler technique problem). Verbal training + the 2 tone trainer (2TT) to achieve a slow inhalation flow rate by encouraging patients to increase the length of their inhalation period. The 2TT is an MDI-like tool without a canister that is designed to give an audible feedback depending on the inhalation speed (a high pitched two tone noise if inhalation is too fast >60l/min). Patients then simulate this technique when using their own MDI. . Duration 6 weeks. Concurrent medication/care: Instucted to practice using the 2TT twice daily before taking their MDI Further details: 1. Additional education training : No education in both groups

	(n=17) Intervention 2: Monitoring inhaler technique + feedback - Visual monitoring + feedback. All patients selected due to a fast inhalation (most common inhaler technique problem). Verbal training to achieve a slow inhalation flow rate by encouraging patients to increase the length of their inhalation period.. Duration 1 visit (6 week follow-up). Concurrent medication/care: nr Further details: 1. Additional education training : No education in both groups
Funding	Principal author funded by industry (Author received sponsorship to carry out studies from several pharmaceutical companies. Research sponsorship also received from EPSRC and MRC)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VERBAL TRAINING PLUS ELECTRONIC DEVICE TO PRACTICE versus VISUAL TRAINING Protocol outcome 1: Quality of life at End of treatment - Actual outcome for Adults and young people (16 years and over): mini AQLQ at 6 weeks; Group 1: mean -0.409 (SD 1.05); n=17, Group 2: mean -0.748 (SD 1.31); n=17; miniAQLQ 1-7 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Lung Function at End of Treatment - Actual outcome for Adults and young people (16 years and over): FEV1 % pred at 6 weeks; Group 1: mean 96.3 % (SD 17.6); n=17, Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Exacerbation (need for OCS) at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Study	Ammari 2013-2[43]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=12)
Countries and setting	Conducted in United Kingdom; Setting: Primary care
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 6 weeks
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Patients with asthma who collected their MDI prescriptions from community pharmacies
Stratum	Children 5 -<16
Subgroup analysis within study	Stratified then randomised: Adults and children
Inclusion criteria	Aged 4-45 years; prescribed at least one MDI without a spacer device including a preventer; identified with poor inhaler technique (defined as poor hand-lung coordination and an IFR ≥90l/min).
Exclusion criteria	Experienced an acute exacerbation of asthma or received OCS within 4 weeks prior to recruitment; had other illnesses adversely affecting their respiratory system; hearing problems and/or unable to distinguish between one and two tones produced by the 2TT tool.
Recruitment/selection of patients	nr
Age, gender and ethnicity	Age - Mean (SD): 10.2 (3.2). Gender (M:F): 8/4. Ethnicity:
Further population details	1. Cognitive function: Not applicable / Not stated / Unclear 2. Disability: Not applicable / Not stated / Unclear 3. Social economic disadvantage: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=6) Intervention 1: Monitoring inhaler technique + feedback - Monitoring using electronic devices + feedback. All patients selected due to a fast inhalation (most common inhaler technique problem). Verbal training + the 2 tone trainer (2TT) to achieve a slow inhalation flow rate by encouraging patients to increase the length of their inhalation period. The 2TT is an MDI-like tool without a canister that is designed to give an audible feedback depending on the inhalation speed (a high pitched two tone noise if inhalation is too fast >60l/min). Patients then simulate this technique when using their own MDI.. Duration 1 visit (6 week follow-up). Concurrent medication/care: Instructed to practice using the 2TT twice daily before taking their MDI Further details: 1. Additional education training : No education in both groups

	(n=6) Intervention 2: Monitoring inhaler technique + feedback - Visual monitoring + feedback. All patients selected due to a fast inhalation (most common inhaler technique problem). Verbal training to achieve a slow inhalation flow rate by encouraging patients to increase the length of their inhalation period.. Duration 1 visit (6 week follow-up). Concurrent medication/care: nr Further details: 1. Additional education training : No education in both groups
Funding	Principal author funded by industry (Author received sponsorship to carry out studies from several pharmaceutical companies. Research sponsorship also received from EPSRC and MRC)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VERBAL TRAINING PLUS ELECTRONIC DEVICE TO PRACTICE versus VERBAL TRAINING Protocol outcome 1: Quality of life at End of treatment - Actual outcome for Children 5 -<16: PAQLQ at 6 weeks; Group 1: mean -0.362 (SD 0.52); n=6, Group 2: mean -0.391 (SD 0.69); n=6; PAQLQ 1-7 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Lung Function at End of Treatment - Actual outcome for Children 5 -<16: FEV1 % pred at 6 weeks; Group 1: mean 90.9 % (SD 14.3); n=6, Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Exacerbation (need for OCS) at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Study (subsidiary papers)	Basheti 2007[123] (Basheti 2008[120])
Study type	RCT (Cluster randomised; Parallel)
Number of studies (number of participants)	(n=)
Countries and setting	Conducted in Australia; Setting: Community - pharmacy education
Line of therapy	Mixed line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Doctor Dx asthma and use of ICS
Stratum	Adults and young people (16 years and over): Aged ≥14 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients presenting with Turbuhaler or Diskus prescriptions for asthma; age ≥14 years; doctor diagnosed asthma; use of ICS with Turbuhaler or Diskus with or without LABA; no change in asthma medication or dose for 1 month.
Exclusion criteria	Did not self-adminisater their own medication; did not speak or understand English.
Recruitment/selection of patients	April 2003 - 2004
Age, gender and ethnicity	Age - Range: ≥14 years. Gender (M:F): nr. Ethnicity:
Further population details	1. Cognitive function: Not applicable / Not stated / Unclear 2. Disability: Not applicable / Not stated / Unclear 3. Social economic disadvantage: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=56) Intervention 1: Monitoring inhaler technique + feedback - Visual monitoring + feedback. Pharmacy trained to deliver education on peak flow meter technique and inhaler technique. Assessed inhaler technique using checklists and then educated using 'show and tell' for each step on the checklist. Incorrect steps on the checklist were highlighted and attached to the patient's inhaler using a label. This was repeated at 1, 2, 3 and 6 months.. Duration 6 months. Concurrent medication/care: nr Further details: 1. Additional education training : No education in both groups (n=56) Intervention 2: No monitoring . Pharmacy trained to deliver education on peak flow meter technique only. Duration 1 visit (6 month follow-up). Concurrent medication/care: nr Further details: 1. Additional education training : No education in both groups

Funding	Principal author funded by industry (Author grant support from GSK and AstraZenica)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VISUAL MONITORING + FEEDBACK versus NO MONITORING OF INHALER TECHNIQUE Protocol outcome 1: Quality of life at End of treatment - Actual outcome for Adults and young people (16 years and over): Marks AQLQ at 3 months; Group 1: mean 0.8 (SD 0.5); n=53, Group 2: mean 1.35 (SD 0.6); n=44; Marks AQLQ 0-10 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people (16 years and over): Marks AQLQ at 6 months; Group 1: mean 0.8 (SD 0.6); n=53, Group 2: mean 1.3 (SD 0.6); n=44; Marks AQLQ 0-10 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Lung Function at End of Treatment - Actual outcome for Adults and young people (16 years and over): PEFv (Min%Max) at 3 months; Group 1: mean 83.8 % (SD 8.3); n=53, Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people (16 years and over): PEFv (Min%Max) at 6 months; Group 1: mean 78.9 % (SD 9.7); n=53, Group 2: mean 74.4 % (SD 8.9); n=44; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Exacerbation (need for OCS) at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

G.21 Tele-healthcare to monitor asthma control

Table 153: Baptist 2013[101]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments

Baptist, A. P., et al. (2013). A randomized controlled trial of a self-regulation intervention for older adults with asthma. May. *Journal of the American Geriatrics Society, 61*(5), 747-753	RCT 1 tertiary care centre in USA	N=70 **Tele:** N=34 **Control:** N=36		**Tele**	**Control**	3 in-person group sessions and 3 one-on-one telephone sessions. Group sessions included seven participants and a health educator who served as the leader. A health educator conducted all group and telephone sessions.	3 phone calls not related to asthma self-management. An allergist called participants randomized to the control group 1 and 2 weeks after enrolment to address any inquiries regarding information received during the asthma education session.	6 and 12 months	Hospital visits	T:0/34 C:4/36	**Funding:** American Academy of Allergy Asthma and Immunology **Risk of bias:** • Randomised with number generator • Participants, physicians and assessors were blind • 90% included in final analysis • ACQ continuous data not reported
			Age, yrs	72.8	73.8				GP visits	T: 6/34 C: 14/36	
			% male:	32.4	13.9				FEV1 % predicted	T: 84.6 C: 76.3 P=0.17	
			% pred. FEV1	84.2	80.9						
			Inclusion criteria: • Outpatients aged 65 and older • Physician diagnosis of asthma • Daily controller medication • Access to a home telephone **Exclusion criteria**: • COPD or any other primary pulmonary disorder • Current smokers or smoking history of > 20 pack-years • Mental impairment								

Table 154: Barbanel 2003[106]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Barbanel, D., Eldridge, S., & Griffiths, C. (2003). Can a	RCT Deprived area	N=24 **Tele:**		**Tele**	**Control**	After a 3-day training course on asthma care, patients were	The control group received no input from	6 months	North of England Asthma Scale – not	N/A	**Funding:** Not stated
			Age, yrs	45	47						

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
self-management programme delivered by a community pharmacist improve asthma control? A randomised trial. *Thorax, 58*(10), 851-854.	of London	N=12 **Control:** N=12	% male:	50	41.7	allocated to a pharmacist for a 45 min educational session and weekly follow-up calls for 3 months. Education included inhaler technique and PEF meter use. Patients were also given supporting literature and a management plan.	the pharmacist.		meta-analysed		• **Risk of bias:** Sequence generation unclear but concealed allocation • Blinding was not possible • One dropout in control was imputed
			Inclusion criteria: • Adults aged 18-65 years • Maintenance ICS **Exclusion criteria:** • Recently attended secondary care with acute asthma • Recent medication change • Acute respiratory infection								

Table 155: Bender 2010[151]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Test of an interactive voice response intervention to improve adherence to controller medications in adults with asthma. Journal of the American	RCT	N=50 (25 in each group) 18 to 65 years; physician-diagnosed asthma for which they were prescribed daily inhaled corticosteroid treatment. Exclusion criteria: (1) any	Mean age treatment: 39.6 (12.8) years; control 43.5 (14.3) years. % male: 40% and 32%. White 56% and 60%; Hispanic 24% and 12%; African American 20% and 20%;	2 automated interactive voice response telephone calls separated by one month, with one additional call if they reported recent symptoms of poorly controlled disease or failure to fill a prescription. Calls were completed in	Participants in the control group received no calls.	10 weeks	Mean ICS adherence (dividing the number of inhaler puffs taken by the number of puffs prescribed to be taken each day and then averaged over the 10-week interval) was	64.5 (17.2) % vs. 49.1 (16.8) %, p=0.0032	Investigator-Sponsored Study Program of AstraZeneca	Randomisation and allocation concealment unclear (random table generated before study initiation); investigator blind; no attrition; no selective

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Board of Family Medicine: 23: 159-165 Bender BG, Apter A, Bogen DK, Dickinson P, Fisher L, Wamboldt FS, and Westfall JM 2010.		significant disease or disorder that, in the opinion of the investigator, might influence the results of the study or the patient's ability to participate in the study (including other chronic health disorders, current substance abuse or dependence, mental retardation, or psychiatric disorder); and (2) current participation in any other asthma-related research or clinical trial.	Asian 0% and 8%. All not significantly different.	< 5 minutes and included content designed to inquire about asthma symptoms, deliver core educational messages, encourage refilling of inhaled corticosteroid prescriptions, and increase communication with providers			higher in the group receiving IVR intervention than in the control group			reporting; groups comparable at baseline
							Change in Beliefs about Medications Questionnaire (scores above 0 indicate more positive beliefs and scores below 0 indicate more negative beliefs): the group receiving IVR intervention demonstrating a greater upward shift in positive medication beliefs	0.248 (1.07) vs. -0.508 (0.913), p=0.007		
							Change in Asthma Quality of Life Questionnaire	-0.152 (0.92) vs. -0.381		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							(higher scores indicate better quality of life)	(1.06), not signifi cant		
							Change in Asthma Control Test (higher scores indicate better control of asthma symptoms)	-1.120 (3.90) vs. -1.840 (4.14), not signifi cant		

Table 156: Chan 2007[297]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Chan, D. S., et al (2007). Internet-based home monitoring and education of children with asthma is comparable to ideal office-based	RCT Child clinic in Hawaii army centre	N=120 **Tele:** N=60 **Control:** N=60		**Tele:**	**Control:**	Virtual group patients received computers, internet connections, and in-home, Internet-based case	Office-based group patients received traditional in-person education and case management.	12 m	Hospital visits	T: 1/60 C: 1/60	**Funding:** US Army Medical Research Acquisition Activity **Risk of bias:**
			Age, yrs	10.2	9				ED visits	T: 4/60 C: 2/60	
			% male	61.7	63.3				PAQLQ child	T: 6.1 (1.1) C: 5.8 (1.2)	
			Inclusion criteria: • Children/teens aged 6-17						PAQLQ parent	T: 6.4 (1) C: 6.2 (0.8)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
care: results of a 1-year asthma in-home monitoring trial. *Pediatrics, 119*(3), 569-578.			• Persistent asthma • Dependent of active duty or retired military personnel • Could receive cable modem • Willing to complete questionnaires **Exclusion criteria:** • Not stated	management and received education through the study website.			FEV1 % predicted	T: 97.4 (19.2) C: 92.7 (18.1)	• Random numbers table • Un-blinded • Dropout much higher in tele-health group (23%) than office group (8%)

Table 157: Chatkin 2006[305]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Chatkin, J. M., et al. (2006). Impact of a low-cost and simple intervention in enhancing treatment adherence in a Brazilian asthma sample. *Journal of Asthma, 43*(4), 263-266.	RCT Physicians from all over Brazil were invited to include their patients	N=271 **Tele:** N=140 **Control:** N=131		**Tele**	**Control**	Participants received 10 minute telephone calls every two weeks to provide asthma education with emphasis on treatment adherence. A specifically trained nursing student conducted the calls.	Routine care with a call at the beginning and end of the study to collect data.	Unknown follow-up	Adherence measures	None of interest	**Funding:** GSK Brazil **Risk of bias:** • Minimal information regarding randomisation • 10 patients were not included because they did not return their
			Age, yrs	43.3	44.4						
			% male	25.7	29						
			Inclusion criteria: • Adults/adolescents • 12+ years • Mod./severe asthma according to GINA **Exclusion criteria:** • Mild persistent asthma								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			• Pregnancy or breast-feeding • Recent alcohol or drug abuse • Active medical condition						drug disks and 8 for not responding to the telephone calls

Table 158: Christakis 2012[322]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Improving parental adherence with asthma treatment guidelines: a randomized controlled trial of an interactive website. Academic pediatrics: 12: 302-311 Christakis DA, Garrison MM, Lozano P,	RCT	N=603; 283 intervention; 320 control. Parents of children aged 2 to 10 years with asthma (at least 1 clinical encounter – clinic visit, emergency room or inpatient admission – or two prescription refills for bronchodilato	29% had mild to severe persistent asthma; 71% had mild intermittent asthma; 54% on at least one controller medication and of these, 61% took controller 5 or more days per week. Among controller users, 60% adherent in control arm and 61% in	Web-based intervention: gathers information from parents (day and night time symptoms, quick-reliever use), applies algorithm to determine asthma severity, home care practices (controller use and adherence), functional status, parental beliefs (outcomes expectation and	Control parents had similar intervention around reducing media usage among their children.	12 months	Appropriate controller use: non-users converted to controller use at 6 months	15.69% control vs. 15.79% int'n, p=0.98 (denominators unclear)	National Heart, Lung and Blood Institute	Computer randomisation; 85% completed 6-month assessment and 80% at 12 months; no selective reporting; groups comparable at baseline
							Patients who should have been on controllers at baseline (i.e. persistent asthma) but were not, who were on controllers at 6	7/19 (36.84%) int'n; 5/30 (16.7%) cont; OR 2.85, 95% CI 0.63 to 14.04,		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Meischke H, Zhou C, and Zimmerman FJ 2012.		rs in the last year) in an HMO and a primary care clinical practice network. Had to have convenient access to internet-enable computer, speak English at home.	intervention arm at baseline.	self-efficacy), feedback on child's asthma (recommendations regarding controller use and other aspects of asthma care), allowed parent to set goals relevant to their situation. Monthly email reminders to log on. Intervention 6 months, then opt-in for further 6 months			months	p=0.17		
							Persistent asthma on controllers at baseline but discontinued at 6 months	6/42 (14%) int'n; 3/58 (5%) cont; OR 0.33, 95% CI 0.05 to 1.67, p=0.16		
							Adherence at 6 months (5 or more days per week) to controllers for those who were prescribed them at 6 months	72% int'n vs. 62% cont, OR 1.54, 95% CI 0.90 to 2.63, p=0.10		
							Adherence at 6 months (5 or more days per week) to controllers for the persistent asthma subgroup who were	77% vs. 50%, OR 3.33, 95% CI 1.20 to 10.07, p=0.01 (denominators		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							prescribed them at baseline and 6 months	unclear)		
							Outcome expectations at 6 months: positive: no difference between groups; negative: lower in intervention arm.	Positive: 124/241 (51%) int'n; 122/274 (44%) cont, p=0.12. Negative: 145/241 (60%) int'n vs. 190/274 (69%) cont, p=0.03		
							Parental self-efficacy (parents somewhat or strongly agreeing that they can give their child controller medication daily) at 6	217/241 (90%) int'n vs. 218/274 (80%) cont, p=0.001		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							months			
							Asthma symptoms and severity at 6 and 12 months: Proportions of children with stable or improved symptoms not significantly differed between groups	Data not shown		
							Proportion of children on controllers at 12 months	50% int'n vs. 57% cont, p=0.17 (denominators unclear)		
							Of those who met severity criteria for controllers at baseline, number on them at 12 months	34/53 (64%) int'n, 50/82 (60%) cont, p=0.86		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							Adherence 5 or more days/week at 12 months	69/105 (66%) int'n, 88/140 (63%) cont, p=0.69		

Table 159: Deschildre 2012[427]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Deschildre, A., et al. (2012). Home telemonitoring (forced expiratory volume in 1 s) in children with severe asthma does not reduce exacerbations. *European respiratory journal, 39*(2), 290-296.	RCT 4 paediatric clinics in France	N=50 **Tele:** N=25 **Control:** N=25		**Tele**	**Control**	Daily home spirometry transmitted to the physician via modem, and medical feedback. Depending on FEV1 results, the GP or hospital paediatrician was contacted.	Conventional treatment	12 m	Hospital visits	T: 2/21 C: 2/23	**Funding:** French Ministry of Health **Risk of bias:** • Unclear randomisation procedures • Un-blinded • Unbalanced attrition (higher in tele group) • Analysed with non-parametric tests
			Age, yrs (median)	11.0	11.2				Oral steroids	T: 19/21 C: 21/23	
			% male	72	76						
			FEV1 % predicted (median)	87.4	83.3						
			Inclusion criteria: • Children/teens aged 6-16 • Severe allergic asthma (3rd Paediatric Asthma Consensus) • Frequent exacerbations • reversibility of > 12%and/or								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			an increase of at least 200 mL • All taking LABA/ICS combo **Exclusion criteria:** • Congenital or acquired illness other than asthma						

Table 160: Donald 2008[443]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Donald, K. J., McBurney, H., Teichtahl, H., & Irving, L. (2008). A pilot study of telephone based asthma management. *Australian Family Physician, 37*(3), 170-173.	RCT 2 teaching hospitals in Australia	N=71 **Tele**: N=36 **Control**: N=35		**Tele:**	**Control:**	6 follow-up calls from the nurse educator about current asthma symptoms, with management advice. Patients were given a PEF meter and recording instructions, a face-to-face session with an asthma nurse educator, advice on medications, triggers and management, and an Asthma Action Plan.	The control group was encouraged to continue with self-management and usual GP care	12 m	Hospital visits	T: 1/31 C: 6/29	**Funding:** Unclear **Risk of bias:** • Unclear randomisation procedures • Researcher blinded, patients and nurses not • Low questionnaire response rate
			Age, years	36.2					ED visits	T: 7/36 C: 5/35	
			% male	23.9					GP visits	T: 22/31 C: 16/29	
			Inclusion criteria: • Adults aged 18-55 • Previous asthma admission • Primary diagnosis of asthma **Exclusion criteria:** • Other chronic respiratory or unstable medical condition • Cognitive disability • Psychiatric illness						Oral steroids Absence (days)	T: 22/31 C: 21/29 T: 2.81 (6.26) C: 5.22 (8.38)	

Table 161: Gruffydd-Jones 2005[597]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Gruffydd-Jones, K., et al (2005). Targeted routine asthma care in general practice using telephone triage. *British Journal of General Practice, 55*(521), 918-923.	RCT 1 general practice in England	N=194 **Tele**: N=97 **Control**: N=97		**Tele:**	**Control:**	Contacted by telephone every 6-months by a trained asthma nurse and asked the RCPs 'three questions' plus two extra questions related to a high risk of asthma death. The nurse formulated an individualised asthma action plan with the patient.	Usual care by 6-monthly check up with an asthma nurse. Symptom scores, inhaler technique, and PEF were checked and all patients issued with an asthma action plan.	6 and 12 m	AQLQ	T: 5.93 (1.64) C: 5.79 (0.90)	**Funding:** Asthma UK **Risk of bias:** • Random number tables • Un-blinded • Unbalanced attrition (higher in usual care)
			Age, years	50.8	49.6				ACQ	T:-0.18 (95% CI) (-0.38 to 0.02) C: -0.11 (-0.32 to 0.11)	
			% male	51.5	39.2				Costs	T: 210.4(95% CI) (208.9 to 211.8) C: 332.7 (329.5 to 335.9)	
			Inclusion criteria: • Adults aged 17-70 • On the practice asthma list **Exclusion criteria**: • Housebound or no phone								

Table 162: Guendelman 2002[602]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Guendelman, S., et al (2002). Improving asthma outcomes and self-management behaviors of	RCT 1 clinic in California, USA	N=134 **Tele**: N=66 **Control**: N=68		Tele:	Control:	Internet-based asthma self-management and education program with feedback (Health Buddy) which asked	Paper asthma diary. All children returned for 2 follow-up visits at 6 and 12 weeks when they received	3 m	Hospital visits	T: 4/62 C: 1/60	**Funding:** Unclear **Risk of bias:** • Unclear sequence generation,
			Age, years	12.0	12.2				ED visits	T: 6/62 C: 11/60	
			% male	61	54						

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
inner-city children: a randomized trial of the Health Buddy interactive device and an asthma diary. *Archives of Pediatrics & Adolescent Medicine., 156*(2), 114-120.			**Inclusion criteria**: • Children/teens aged 8-16 • Persistent asthma • English speaking with a telephone in the house **Exclusion criteria**: • In another asthma study • Mental or physical challenges that affected the program • Co-morbid conditions that might affect quality of life	every day about asthma status, PEF and medication. Responses were downloaded to the nurse co-ordinator overnight.	further standardised teaching from the nurse co-ordinator				concealed with envelopes • Un-blinded • Low attrition

Table 163: Gustafson 2012[610]

Reference	Study type	Number of patients	Patient characteristics	Tele:	Control:	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Gustafson, D., et al (2012). The effects of combining web-based eHealth with telephone nurse case management for pediatric asthma control: A randomized	RCT USA	N=301 **Tele**: N=132 **Control**: N=127	Age, years	7.7	8.2	Automated management software with monthly calls from nurse (CHESS+CM). Based on self-determination theory and designed to improve competence, social support,	Treatment as usual plus asthma information	12 m	ACQ	MD -0.31; 95% CI -0.56 to -0.06; 0=0.01	**Funding:** National Institute of Nursing Research **Risk of bias:** • Sequence generation fine and well concealed • Un-blinded
			% male	66	57						
			Baseline ACQ	2.49	2.32						

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
controlled trial. [References]. *Journal of medical Internet research, 14*(4), 41-59.			**Inclusion criteria**: • Children aged 4-12 • Diagnosis of asthma or wheezing • Controller meds and poor adherence **Exclusion criteria**: • Not described	and intrinsic motivation of parents and children.					• Balanced attrition

Table 164: Halterman 2012[626]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Halterman Jill, S. et al (2012). Working toward a sustainable system of asthma care: Development of the School-Based Preventive Asthma Care Technology (SB-PACT) trial. *49*, 395-400	RCT 19 inner-city schools in New York, USA	N=100 **Tele**: N=48 **Control**: N=51		**Tele:**	**Control:**	'SB-PACT' intervention: web-based screening, electronic communication with primary care providers, online prescription of medications, direct nurse observation of adherence in schools, assessment of symptoms online	In addition to usual care, families in both groups were provided with written educational hand-outs on asthma triggers, treatment, and local asthma resources	8 m	Hospital visits	T: 1/48 C: 1/51	**Funding:** National Heart, Lung, and Blood Institute of the National Institutes of Health **Risk of bias:** • Sequence generation fine and well concealed • Families not blind, but assessors were
			Age, years	7.5	7.0				ED visits	T: 4/48 C: 3/51	
			% male	52	63				GP visits	T: 6/48 C: 8/51	
									AQLQ	T: 6.46 (0.7) C: 6.31 (0.9)	
			Inclusion criteria: • Children aged 3-10 years • Persistent asthma (physician diagnosed base on NHLBI) **Exclusion criteria:** • Non English speaking, no access to phone • Other significant conditions						School absence		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
									• No dropout

Table 165: Jan 2007[749]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Jan, R. L., et al. (2007). An internet-based interactive telemonitoring system for improving childhood asthma outcomes in Taiwan. Telemedicine Journal and e-Health, 13(3), 257-268.	RCT 1 university medical center in Taiwan	N=164 **Tele**: N=88 **Control**: N=76		**Tele:**	**Control:**	"Blue Angel for Asthma Kids", an Internet-based paediatric asthma monitoring program children and parents. Included symptom and PEF diaries and Asthma Action Plans based on the GINA. Data could be shared with the physician who gave feedback by phone/email.	Traditional treatment in an outpatient allergy and asthma clinic accompanied by a PEF meter and diary. Also received verbal and printed asthma education and an Action Plan as part of usual care.	3 m	PEF morning	T: 18.7 (49.4) C: 10.9 (40)	**Funding:** National Science Council and Bureau of Health Promotion **Risk of bias:** • Unclear sequence generation, concealed with envelopes • Un-blinded • Low attrition
			Age, years	10.9	9.9				PEF evening	T: 23.1 (56.5) C: 11.1 (41.6)	
			% male	39.7	36.8						
			Inclusion criteria: • Children aged 6-12 years • Access to internet • Physician-diagnosed asthma **Exclusion criteria:** • Other chronic conditions such as broncho-pulmonary dysplasia								

Table 166: Khan 2004[849]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Khan, M. S. R., et al (2004). Randomized controlled trial of asthma education after discharge from an emergency department. Journal of Paediatrics & Child Health, 40(12), 674-677.	RCT 1 centre in Sydney, Australia	N=310 **Tele**: N=155 **Control**: N=155		**Tele:**	**Control:**	Parents received a telephone call by an asthma nurse educator within 2 weeks of discharge to reiterate advice given at discharge. Calls lasted an average of 13 min (range 5 to 44 minutes).	All parents received written materials with facts about asthma, use of spacers, management of exercise induced asthma and when to contact a doctor.	6 m	Hospital visits	T: 0/136 C: 0/130	**Funding:** Financial Markets Foundation for Children **Risk of bias:** • Random numbers table • Assessors blind • Possible attrition bias
			Age, years	4.9					ED visits	T: 1/136 C: 0/130	
			% male	65.5							
			Inclusion criteria: • Children aged 1-15 years • Recent ED discharge **Exclusion criteria:** • Non English speaking								

Table 167: Liu 2011[1020]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Liu, W. T., et al (2011). A mobile telephone-based interactive self-care system improves asthma control.	RCT Clinics at a teaching hospital in Taiwan	N=89 **Tele**: N=60 **Control**: N=60		**Tele:**	**Control:**	Mobile phone-based software: with electronic diary to record symptom score, reliever use, and lung function. Staff reviewed data uploaded to website and gave advice in	Written asthma diary and action plan. All subjects received asthma education, self-management plan, and	6 m	Mortality	T: 0/43 C: 0/46	**Funding:** Unclear **Risk of bias:** • Allocation not described • Un-blinded • High attrition
			Age, years	50.4	54				Hospital visits	T: 0/43 C: 1/46	
			% male	51.2	47.8				ED visits	T: 2/43 C: 12/46	
			Inclusion criteria: • Adults						FEV1 % predicted	T: 65.2 (21) C: 56.5 (19)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
European respiratory journal, 37(2), 310-317			• Moderate/severe asthma	accordance with GINA guidelines. Data were given to the doctors to adjust treatment plans.	standard treatment		PEF L/min	T: 382.7 (56) C: 343.5 (52)	

Table 168: Ostojic 2005[1278]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Ostojic, V., et al. (2005). Improving asthma control through telemedicine: A study of short-message service. *Telemedicine Journal & E-Health, 11*(1), 28-35.	RCT 1 clinic in Croatia	N=16 **Tele**: N=8 **Control**: N=8		**Tele:**	**Control:**	Paper diary for PEF, medication use and symptoms. PEF (3 times a day), sent results to a computer in the asthma centre and received weekly text instructions from an asthma specialist about therapy or the need for extra office visits.	Both groups were treated according to GINA guidelines. Controls also kept a daily diary of PEF and symptoms, but results were only reviewed by the physician at the end of the study period.	4 m	Hospital visits	T: 2/8 C: 7/8	**Funding:** Unclear **Risk of bias:** • Computer randomised • Un-blinded • No dropouts
			Age, years	24.8	24.5				FEV1 % predicted	T: 81.3 (17.3) C: 78.3 (21.1)	
			% male	63	50						
			% predicted FEV1	77.6	78.9						
			Inclusion criteria: • Adults with moderate asthma • All using LABA/ICS **Exclusion criteria:** • Adults with moderate asthma • All using LABA/ICS								

Table 169: Pinnock 2003[1348]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Pinnock, H., et al (2003). Accessibility, acceptability, and effectiveness in primary care of routine telephone review of asthma: pragmatic, randomised controlled trial. *BMJ, 326*(7387), 477-479.	RCT 4 UK GPs	N=278 **Tele**: N=137 **Control**: N=141		**Tele:**	**Control:**	Telephone review with the asthma nurse. The nurse tried up to 4 times to contact the patients.	Face-to-face reviews in the surgery also with the asthma nurse, one invitation was sent in the usual manner. Content of the review was as the nurse deemed appropriate.	Variable follow-up, pragmatic design	Hospital visits	T: 0/137 C: 0/141	**Funding:** Educational grant from AstraZeneca **Risk of bias:** • Centrally randomised • Un-blinded
			Age, years	54.6	56.4				ED visits	T: 0/137 C: 0/141	
			% male	41	42				Oral steroid use	T: 5/137 C: 3/141	
			Baseline AQLQ	5.17	5.16				GP visits	T: 27/137 C: 34/141	
			Inclusion criteria: • Adults aged 18+ • Asthma for 1 year + • Bronchodilator prescription in previous 6 months **Exclusion criteria**: • COPD • Communication difficulties						AQLQ	T: 5.15 (1.28) C: 5.52 (1.14)	

Table 170: Pinnock 2007[1347]

Reference	Study type	Number of patients	Patient characteristics				Intervention	Comparisons	Length of follow-up	Outcome measures	Effect sizes	Comments
Pinnock H., et al (2007). Accessibility, clinical effectiveness and practice costs of providing a telephone	RCT 1 UK GP over 3 sites	N=1728 **Tele**: N=554 **Control1**: N=515		**Tele**	**Cont 1**	**Cont 2**	Sent 3 invitations over the study period to book either a phone or face-to-face review both at a pre-arranged	1) Usual care maintained their well-established asthma clinic but no re call was undertaken. 2) Patients were recalled to face-	12 m	AQLQ	T: 5.29 (1.2) C1: 5.27 (1.2) C2: 5.31 (1.2)	**Funding:** Scientific Foundation Board of the RCGP **Risk of bias:** • Randomised
			Age, yrs	43	45.4	42.3				ACQ	T: 1.20 (1) C1: 1.24 (1) C2:1.33 (1.1)	
			% male	44.2	44.7	44.9				Cost total	T: £3982 C1: £3340	

Reference	Study type	Number of patients	Patient characteristics				Intervention	Comparisons	Length of follow-up	Outcome measures	Effect sizes	Comments
option for routine asthma reviews: phase IV controlled implementation study. *British Journal of General Practice*, *57*(542): 714–722		**Control2**: N=659					time. Patients who did not respond to the 3 invitations were phoned and reviewed opportunistically	to-face reviews using invitations by post or with repeat prescriptions. There was no option for a phone review and no attempt to contact non-attenders.			C2: £4485	with coin toss • Un-blinded
			% with COPD	6.5	7.2	8.5				Cost per review	T: £10.03 C1: £11.85 C2: £12.74	
			Inclusion criteria: • Adults aged 12+ years • Prescription in previous year **Exclusion criteria:** • Diagnosis of COPD									

Table 171: Prabhakaran 2009[1377]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Prabhakaran, L., et al (2010). The use of text messaging to improve asthma control: A pilot study using the mobile phone short messaging service (SMS). *Journal of telemedicine and telecare, 16*(5), 286-290	RCT Hospital in Singapore and location	N=120 **Tele**: N=60 **Control**: N=60		**Tele:**	**Control:**	SMS monitoring to assist with the management of their asthma control for three months.	All patients were seen by a trained asthma nurse educator who assessed their asthma control, compliance and inhaler technique prior to asthma education. The 60 patients in the control group were left to self-manage their asthma for	3 m	Mortality	T: 0/60 C: 0/60	**Funding:** Unclear **Risk of bias:** • Randomised with slips of paper • Un-blinded • Low dropout
			Age, years	37	40				Dichot. ACT, can't use		
			% male	35	47						
			Inclusion criteria: • Adults aged 21+ years • Previous asthma admission • English speaking and able to use a mobile phone **Exclusion criteria:** • Significant co-morbidity								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			• Mild asthma		three months				

Table 172: Rasmussen 2005[1421]

Reference	Study type	Number of patients	Patient characteristics				Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Rasmussen, L. et al. (2005). Internet-based monitoring of asthma: A long-term, randomized clinical study of 300 asthmatic subjects. *Journal of Allergy & Clinical Immunology, 115*(6), 1137-1142.	RCT Copenhagen Denmark	N=300 **Tele**: N=100 **Control1**: N=100 **Control2**: N=100		**Tele**	**Cont 1**	**Cont 2**	Electronic diary, an asthma action plan and a decision support system for the physician. Patients were given a PEF Meter and taught how to fill in a daily diary and respond to the computer's advice. Physicians gave instructions via e-mail or telephone.	1) Specialists taught patients how to adjust medication on the basis of a PEF meter and written action plan 2) Patients were asked to contact their GP and pass on a letter describing the study and giving the test results. GPs in Copenhagen had been sent a circular about asthma and GINA guidelines.	12 m	Hospital visits	T: 0/85 C1: 1/88 C2: 0/80	**Funding:** Grants from H:S Corporation of University Hospital of Copenhagen, AstraZeneca, and private funds **Risk of bias:** • Randomised consecutively with sealed envelopes • Un-blinded • Unbalanced dropout • Some selective reporting
			Age, yrs	28	30	30				ED visits	T: 2/85 C1: 0/88 C2: 1/80	
			% male	31.8	34.1	37.5				GP visits	T: 3/85 C1: 2/88 C2: 1/810	
			% pred FEV1	91	93	92						
			Baseline AQLQ	6.2	6.2	6.1				FEV1 change (mL)	T: 187 (369) C1: 35 (281) C2: 4 (268)	
			Inclusion criteria: • Adults aged 18-45 years • Asthma according to ATS **Exclusion criteria:** • Not described									

Table 173: Ryan 2012[1478]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Ryan, D., et al (2012). Clinical and cost-effectiveness of mobile phone supported self-monitoring of asthma: multicentre randomised controlled trial. *BMJ (Online), 344*(7854), e1756.	RCT 32 GPs in England	N=288 **Tele**: N=145 **Control**: N=143		**Tele:**	**Control:**	Twice daily recording and mobile phone based transmission of symptoms, drug use, and peak flow with immediate feedback prompting action according to an agreed plan	Paper-based monitoring with the same clinical care as the intervention group (BTS/SIGN based). Both groups also received a 30 minute education session from the practice nurse before randomisation .	6 m	Hospital visits	T: 3/140 C: 1/141	**Funding:** Asthma UK **Risk of bias:** • Centrally randomised • Blinded outcome assessment
			Age, years	46.6	51.5				ED visits	T: 3/140 C: 0/141	
			% male	33.8	41.3				GP visits	T: 51/140 C: 41/141	
			Baseline ACQ	2.32	2.29				Oral steroid use	T: 28/140 C: 30/141	
			Inclusion criteria: • Adults aged 12+ • Poorly controlled asthma **Exclusion criteria:** • Other lung disease or other clinical/social problems						AQLQ	T: 5.00 (1.32) C: 4.99 (1.34)	
									ACQ	T: 1.57 (0.99) C: 1.56 (1.09)	

Table 174: Seid 2012[1541]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Seid, M., et al (2012). The In Vivo adherence intervention for at risk adolescents with asthma: Report of a randomized	RCT 1 site in Cincinnati, USA	N=26 **Tele**: N=14 **Control**: N=14		**Tele:**	**Control:**	Asthma education, in-person motivational interviewing and problem solving skills training, cell phone with	Asthma education and cell phone without tailored text messaging	1 and 3 m	None of interest	N/A	**Funding:** National Institutes of Health **Risk of bias:** • Random number tables
			% male	41.7	21.4						
			Inclusion criteria: • Adolescents aged 12-18 years • Moderate/severe asthma								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
pilot study. *Journal of pediatric psychology, 37*(4), 390-403			(NHLBI) • Symptoms in past 2 weeks **Exclusion criteria:** • Co-morbid conditions • Non English speaking	tailored text messages					• Blinded outcome assessment • Pilot study

Table 175: van der Meer 2009[1803]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Van Der Meer, V., et al (2010). Self-management for asthma on the Internet: A randomized study. *Nederlands tijdschrift voor geneeskunde, 154*(9), 403-409.	RCT 37 GPs in Holland	N=200 **Tele**: N=101 **Control**: N=99		**Tele:**	**Control:**	Website to record FEV1 (daily), ACQ (weekly), and symptoms via internet or text. Also included asthma treatment plan and online education. Patients could contact an asthma nurse when needed. The ACQ score fed into an algorithm and patients received one of 4 treatment messages.	Control patients had access to the part of the website on which a diary of symptoms and exacerbations was kept.	12 m	AQLQ change with 95% CI	T: 0.56 (0.43 to 0.68) C: 0.18 (0.05 to 0.31)	**Funding:** Unclear **Risk of bias:** • Computer randomisation • Un-blinded • Completer analysis
			Age, years	36	37				ACQ change with 95% CI	T: -0.54 (-0.65 to -0.42) C: -0.06 (-0.18 to 0.05)	
			% male	32	29						
			% predicted FEV1	88	90						
			Baseline ACQ	1.12	1.11						
			% taking LABA/ICS	59	60						
			Inclusion criteria: • Adults aged 18-50 years • ICS for > 3 months in the past year **Exclusion criteria:** • Currently on oral steroids								

Table 176: Vollmer 2006[1852]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Vollmer, W. M., et al (2006). Use and impact of an automated telephone outreach system for asthma in a managed care setting. *American Journal of Managed Care, 12*(12), 725-733.	RCT Large group health organisation in Oregon, USA	N=6948 **Tele**: N=3389 **Control**: N=3367		**Tele:**	**Control:**	Three phone calls 5 months apart with tailored advice to address recent ED care, asthma control and medication use. Optional tailored feedback. The call generated alerts for the provider as to which patients were at high risk of exacerbations.	Routine care with no telephone calls	10 m	AQLQ (in a subset of patients)	T: 5.2 (1.2) C: 5.1 (1.2)	**Funding:** Centres for Disease Control and Prevention and the Kaiser Permanente Care management Institute **Risk of bias:** • No details about randomisation or blinding • Some data only collected from a subset of patients
			Age, years	51.8	51.4				Hospital visit *or* ED visit	T: 132/3220 C: 121/3033	
			% male	35	35						
			Baseline AQLQ	5.0	5.2						
			Inclusion criteria: • Adults aged 18+ years • At least 180 days of asthma medication dispensed **Exclusion criteria:** • COPD								

Table 177: Willems 2007[1895]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Willems, D. C., et al (2007). Process evaluation of a nurse-led telemonitoring	RCT Single centre in the Netherl	N=109 **Tele**: N=55 (26 adults, 29		**Tele:**	**Control:**	Asthma tele-monitoring via home modem. Patients were asked to perform daily	Regular outpatient care: 3 to 6-monthly medical check-ups by	12 m	AQLQ	T: 5.73 (1.09) C: 5.48 (1.18)	**Funding:** Unclear Baseline characteristics reported for
			Age, years	27.2	28.4				ED visits	T: 0/55 C: 4/54	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
programme for patients with asthma. *Journal of Telemedicine & Telecare, 13*(6), 310-317.	ands	children) **Control**: N=54 (27 adults, 27 children)	% male	58.2	44.4	PEFR and more often in exacerbations. The nurse could increase and decrease asthma medication and involve a doctor if necessary.	their lung specialist or paediatrician				children and adults separately, but not outcome data **Risk of bias:** • Random number list, stratified by age • Un-blinded • Compliance for AQLQ and PEF was low
			% predicted FEV1	94.9	96.0						
			Inclusion criteria: • Adults and children aged 7+ • Stage I to III GINA **Exclusion criteria:** • Severe co-morbidity								

Table 178: Xu 2011[1925]

Reference	Study type	Number of patients	Patient characteristics	Tele:	Control:	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Xu, C., et al (2010). A randomized controlled trial of an interactive voice response telephone system and specialist nurse support for childhood	RCT Child hospitals in Australia	N=121 (82) in relevant groups) **Tele**: N=41 **Control**: N=41				1) Interactive Voice Response 2) The nurse support group received follow-up calls from one Nurse Specialist every 2 weeks. Where families	Patients' primary care physicians were notified and continued to provide primary asthma care. All families had the same initial asthma education with	6 m	Hospital visits	T1: 4/39 T2: 4/38 C: 4/40	**Funding:** Unclear **Risk of bias:** • Randomisation unclear • Un-blinded • Low dropout
			Age, years	T1: 7.0 T2: 6.5	7.4				ED visits	T1: 6/39 T2: 8/39 C: 5/40	
			% male	T1: 56.4 T2: 51.2	51.2				Oral steroid use	T1: 16/39 T2: 22/41 C: 21/40	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
asthma management. *Journal of asthma, 47*(7), 768-773			**Inclusion criteria:** • Children/teens aged 3-16 • Recent exacerbation **Exclusion criteria:** • Not described	preferred email contact, the nurse used email to collect the same data and offer education and advice on asthma. 2)	the same Specialist Nurse.		School days lost (yes/no)	T1: 20/38 C: 22/39	
							Parent work days lost (yes/no)	T1: 13/39 C: 13/39	
							AQLQ (child), mean (SD)	T1: 1.1 (1.1) C: 0.5 (0.9)	
							AQLQ (carer), mean (SD)	T1: 1.2 (1.6) C: 1.0 (1.5)	

Table 179: Young 2012[1941]

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Young, H. N., et al (2012). Patient and phaRmacist telephonic encounters (PARTE) in an underserved rural patient population with	RCT Wisconsin, USA	N=98 **Tele**: N=49 **Control**: N=49		**Tele:**	**Control:**	Telephone consultation from pharmacists regarding their asthma self-management and medication use. Five pharmacists	Usual care, which included mail receipt of a prescription refill with written medication use instructions.	Unknown follow-up	None of interest	N/A	**Funding:** National Centre for Research Resources, National Institutes of Health **Risk of bias:**
			Age, years	45.4	43.7						
			% male	26.5	20.4						
			Inclusion criteria: • Adults aged 19+ • Community Health Access								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
asthma: results of a pilot study. *Telemedicine journal and e-health, 18*(6), 427-433			program (uninsured or underinsured people) • Diagnosis of asthma and 1+ asthma medications within 6 months **Exclusion criteria:** • Enrolment in the FHC pharmacy program	incorporated the intervention into their usual practice.					• No randomisation details • Blinded assessment • Balanced dropout • No relevant outcomes

Appendix H: Economic evidence tables

H.1 Monitoring: Tele-healthcare

Table 180: Gruffydd-Jones 2005[597]

Gruffydd-Jones K, Hollinghurst S, Ward S, Taylor G. Targeted routine asthma care in general practice using telephone triage. British Journal of General Practice. 2005; 55:918-923.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CCA (health outcome: Mini-AQLQ scores) **Study design:** Within-trial analysis (RCT) **Approach to analysis:** Analysis of individual level data for asthma control and resource use with unit costs applied. **Perspective:** UK NHS **Time horizon:** 12 months **Treatment effect duration:** 12 months **Discounting:** Not Applicable	**Population:** Adult Asthma Patients **Patient characteristics:** N (control): 62 N (intervention): 84 Mean age (control): 49.6 (SD: 16.1) Mean age (intervention): 50.8 (SD: 15.4) Male (control): 39% Male (intervention): 51% **Intervention 1:** Clinic Group: Patients received 'usual' care by 6 monthly check-up via dedicated asthma nurse. **Intervention 2:**	**Total costs (mean per patient):** Intervention 1: £333.85 (SD: 410.64) Intervention 2: £209.85 (SD: 220.94) Incremental (2−1): Bootstrapped cost difference: £122.35 (p-value: 0.071) **Currency & cost year:** 2004 UK pounds **Cost components incorporated:** Total routine care (minutes) Number of inhalers Number of tablets Non-routine consultations Length of inpatient stays	**Mini-AQLQ score (median per patient at 12 months):** Intervention 1: 5.93 (IQR: 2.07) Intervention 2: 6.47 (IQR: 1.22) Incremental (2−1): NR, though the difference in health was not clinically significant	**ICER (Intervention 2 versus Intervention 1):** Telephone reviews dominated clinical reviews (lower costs and higher health outcomes) **Analysis of uncertainty:** NR

	Telephone group: patients contacted by telephone at 6 monthly intervals by one or two trained asthma nurses. Patient was asked RCP Morbidity Index and if 'yes' was answered to any of the three questions a clinical asthma review was arranged. If asthma was deemed stable for 3 months telephone interviews were resumed.			

Data sources

Health outcomes: Mini AQLQ score.

Quality-of-life weights: NR

Cost sources: Resource use from within RCT;

resources use priced using: BNF; NHS Reference costs; PSSRU 2003

Comments

Source of funding: Research grant from Asthma UK. **Limitations:** Short time horizon of 12 months may not be long enough to capture adverse health impacts and therefore not give an accurate representation of long term health and cost outcomes. Health was also not measured using QALYs, only quality of life not length was considered. Lack of any sensitivity analysis reduces robustness of results.

Overall applicability[(a)]: Partially applicable Overall quality[(b)]: Potentially serious limitations

Abbreviations: CCA: cost–consequence analysis; CI: 95% confidence interval; ICER: incremental cost-effectiveness ratio; NR: not reported; QALYs: quality-adjusted life years, SD: Standard Deviation

(a) Directly applicable / Partially applicable / Not applicable

(b) Minor limitations / Potentially serious limitations / Very serious limitations

Table 181: Ryan 2012[1478]

Ryan D, Price D, Musgrave SD, Malhotra S, Lee AJ, Ayansina D et al. Clinical and cost-effectiveness of mobile phone supported self monitoring of asthma: multicentre randomised controlled trial. BMJ. 2012; 344:e1756.

Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
Economic analysis: CCA (health outcome: changes in scores on asthma control questionnaire and self-efficacy) **Study design:** One year multicentre randomised controlled trial conducted in a UK primary care setting - Within trial analysis **Approach to analysis:** Economic evaluation based on the results of the randomised controlled trial **Perspective:** UK NHS **Time horizon:** 12 months **Treatment effect duration:** 12 months **Discounting:** NA	**Population:** 288 adolescents and adults with poorly controlled asthma (ACQ score ≥ 1.5) **Patient characteristics:** N (control) =142 N (intervention) =145 Mean age (control): 51.5 (SD: 17.7) Mean age (intervention): 46.6 (SD: 18) Male (control): 34% Male (intervention): 41% **Intervention 1:** Mobile phone monitoring: Twice daily recording and mobile phone based transmission of symptoms, drug use, and peak flow with immediate feedback (through t+ Asthma mobile application) prompting action to agreed plan. **Intervention 2:** Patients asked to keep a paper diary, recording the same information gathered from intervention 1	**Total costs (mean per patient):** Intervention 1: £315 (SD: 226) Intervention 2: £245 (SD: 201) Incremental (2−1): £70 (CI: £20 to £121; p = 0.006) **Currency & cost year:** 2008-2009 UK pounds **Cost components incorporated:** Cost of delivering intervention Nursing costs Tele-monitoring service costs Cost of healthcare provision GP respiratory consultations Practice nurse respiratory consultations Secondary care costs (outpatient and admissions) Emergency services Total cost of prescriptions from respiratory drugs	**QALYs (mean per patient):** There was no significant change in asthma control or self-efficacy between the two interventions	**ICER (Intervention 2 versus Intervention 1):** NR **Analysis of uncertainty:** No sensitivity analysis was conducted

	(symptoms, drug use, and peak flow readings twice daily).			
Data sources				
Health outcomes: Self-reported from patients who participated in the trial. **Cost sources:** Unit costs for all resources used by patients in the randomized controlled trial were obtained from the data sources in the UK including the NHS Reference costs (2007-2008), the Personal Social Services Research Unit (2008) and the British National Formulary (BNF 2008).				
Comments				
Source of funding: Asthma UK. **Limitations:** Short time horizon of 12 months may not be long enough to capture adverse health impacts and therefore not give an accurate representation of long term health and cost outcomes. Health was also not measured using QALYs, only quality of life not length was considered. Lack of any sensitivity analysis reduces robustness of results.				
Overall applicability[(a)]: partially applicable **Overall quality[(b)]:** potentially serious limitations				

Abbreviations: CCA: cost–consequence analysis; 95% CI: 95% confidence interval; ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) Directly applicable / Partially applicable / Not applicable

(b) Minor limitations / Potentially serious limitations / Very serious limitations

Table 182: Willems 2007[1896]

Willems DC, Joore MA, Hendriks JJ, Wouters EF, Severens JL. Cost-effectiveness of a nurse-led telemonitoring intervention based on peak expiratory flow measurements in asthmatics: results of a randomised controlled trial. Cost-effectiveness and Resource Allocation. Netherlands 2007; 5:10.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** One year single centre randomised controlled trial – Within trial analysis **Approach to analysis:**	**Population:** Outpatients with asthma **Patient characteristics:** N (Control) = 53 N (Intervention) = 56 Mean age (control over 18 years old): 45.9 (SD: 15.9) Mean age (intervention over	**Total costs (mean per patient):** Intervention 1 (over 18 years old): £1,197 (SD: £1212) Intervention 1 (between 7 and 18 years old): £409 (SD: £591) Intervention 2 (over 18 years old): £1,550 (SD: £1,101)	**QALYs (mean per patient):** Intervention 1 (between 7 and 18 years old): 0.0 (95% CI: 0.00 to 0.02) Incremental (2−1) (Over 18 years old): 0.03 (95% CI: 0.00 to 0.07)	**ICER (Intervention 2 versus Intervention 1) (over 18 years old):** £10693 per QALY gained (pa) 95% CI: NR Probability Intervention 2 (adults) cost-effective (£20K/30K threshold): NR **ICER (Intervention 2 versus Intervention 1) (between 7 and 18 years old):** £40865 per QALY gained (pa)

Comparison of health outcomes and costs between tele-monitoring and usual care. **Perspective:** Dutch societal or healthcare perspective (only healthcare perspective results shown) **Time horizon:** 12 months **Treatment effect duration:** 12 months **Discounting:** NR	18 years old): 45.65 (SD: 11.3) Mean age (control between 7 and 18 years old): 10.85 (SD: 2.3) Mean age (intervention between 7 and 18 years old): 10.57 (SD: 2.1) Male (control over 18 years old): 33.3% Male (intervention over 18 years old): 42.3% Male (control between 7 and 18 years old): 55.6% Male (intervention between 7 and 18 years old): 72.4% **Intervention 1:** Regular outpatient care. Three to six monthly medical check-ups by their lung specialist or paediatrician. For exacerbations patients received additional care by GP and/or outpatient care. **Intervention 2:** Patients received an asthma monitor and had a hospital based nurse practitioner as the main caregiver. Patients were instructed to perform daily lung function tests in	Intervention 2 (between 7 and 18 years old): £830 (SD: £405) Incremental (2−1) (over 18 years old): £353 (95% CI: -£114 to £1118; p=NR) Incremental (2−1) (between 7 and 18 years old): £421 (95% CI: £319 to £862; p=NR) **Currency & cost year:** 2002 Euros (presented here as 2002 UK pounds[(a)]) **Cost components incorporated:** General practitioner practice: (GP visit, GP telephone visit, assistant visit, assistant telephone visit, nurse practitioner visit) Hospital care: (day admission, emergency room visit, surgical procedures, diagnostic procedures, laboratory research, lung specialist outpatient visit, paediatric lung specialist	Incremental (2−1) (between 7 and 18 years old): 0.01 (95% CI: 0.00 to 0.02) Incremental (2−1) (Over 18 years old): 0.03 (95% CI: 0.00 to 0.07)	95% CI: NR Probability Intervention 2 (children) cost-effective (£20K/30K threshold): NR **Analysis of uncertainty:** Using SF-36 instead of EQ-5D leads to drastically different results making the intervention dominated for adults; SF-6D was not assessed in children. Sensitivity analysis was conducted by excluding monitor device costs from the intervention (monitor, modem, batteries and insurance) which equated to £313. This reduced the ICER for adults to £1224 and for children to £10502. This shows that initial capital costs significantly drive the cost-effectiveness result. Therefore in the long run assuming recurrent capital costs will fall the ICER will fall over time, all other things remaining equal.

	the morning and evening and more often when they were having symptoms. Patients asked to transfer data once a month or more with symptoms. Based on data nurse was able to decrease asthma medication (after three months of stable asthma) or increase (if asthma was unstable) by one step.	outpatient visit, asthma nurse practitioner outpatient visit, other medical specialists outpatient visit) Other healthcare professional costs: (speech therapist, homoeopath, company medical officer) Prescribed medication: (medication, pharmacist fee) Professional home care Intervention costs		
Data sources				
Health outcomes: Taken from the results from the in-trial randomized controlled trial. **Quality-of-life weights:** EQ-5D, UK tariff. **Cost sources:** Volumes of hospital care were obtained from the hospital billing system of the university hospital Maastricht. All other resource costs use obtained from cost diaries. Dutch manual for cost research used for unit prices.				
Comments				
Source of funding: NR. **Limitations:** The costs are not from a UK perspective and therefore may not be generalizable. The time horizon is also very short at 12 months; this may not be enough time to capture rare adverse events that would have a differential probability of occurring across the two groups. The results are extremely sensitive to the choice of HRQoL measure used.				
Overall applicability[(a)]: Partially applicable Overall quality[(b)]: Potentially serious limitations				

Abbreviations: 95% CI: 95% confidence interval; CUA: cost–utility analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); HRQoL: Health related quality of life; ICER: incremental cost-effectiveness ratio; NR: not reported; QALYs: quality-adjusted life years; SF-6D: Short form 6 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death)

(a) Converted using 2002 purchasing power parities[1272]

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I: GRADE tables

I.1 Monitoring: Questionnaires

Table 183: Clinical evidence profile: Children (5-16 years) with uncontrolled asthma: Monitoring questionnaires + treatment vs UC + treatment.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Children with uncontrolled asthma: Monitoring control + treatment	UC + treatment	Relative (95% CI)	Absolute		
QOL (< 6months) (follow-up 3 months; measured with: PAQLQ; range of scores: 1-7; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	46	44	-	MD 0.4 higher (0.17 to 0.63 higher)	⊕OOO VERY LOW	CRITICAL
QOL (≥ 6months) (follow-up 12 months; measured with: PAQLQ; range of scores: 1-7; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	46	44	-	MD 0.05 lower (0.5 lower to 0.4 higher)	⊕⊕OO LOW	CRITICAL
Exacerbations (≥ 6months) (follow-up 12 months; assessed with: Course of OCS)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	6/35 (17.1%)	15%	RR 1.14 (0.41 to 3.22)	21 more per 1000 (from 89 fewer to 333 more)	⊕OOO VERY LOW	CRITICAL
Asthma control (< 6months) (follow-up 3 months; measured with: ACQ; range of scores: 0-6; Better indicated by lower values)												
1	randomised	very	no serious	no serious	no serious	none	46	44	-	MD 0.32 lower (0.56 to 0.08	⊕⊕OO	CRITICAL

	trials	serious[1]	inconsistency	indirectness	imprecision					lower)	LOW	
Asthma control (≥ 6months) (follow-up 12 months; measured with: ACQ; range of scores: 0-6; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	46	44	-	MD 0.05 lower (0.35 lower to 0.25 higher)	⊕⊕OO LOW	CRITICAL
Lung function (< 6months) (follow-up 3 months; measured with: FEV1 L; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	46	44	-	MD 0.23 higher (0.08 to 0.38 higher)	⊕OOO VERY LOW	IMPORTANT
Lung function (≥ 6months) (follow-up 12 months; measured with: FEV1 L ; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	46	44	-	MD 0.1 higher (0.11 lower to 0.31 higher)	⊕OOO VERY LOW	IMPORTANT
Symptom free days (< 6months) (follow-up 3 months; measured with: % over 2 weeks ; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	46	44	-	MD 1.5 lower (14.5 lower to 11.5 higher)	⊕OOO VERY LOW	IMPORTANT
Symptom free days (≥ 6months) (follow-up 12 months; measured with: % over 2 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	46	44	-	MD 4 higher (9.7 lower to 17.7 higher)	⊕OOO VERY LOW	IMPORTANT
ICS use (< 6months) (follow-up 3 months; measured with: mean daily dose ug; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	46	44	-	MD 14 higher (79 lower to 107 higher)	⊕OOO VERY LOW	IMPORTANT

ICS use (≥ 6months) (follow-up 12 months; measured with: mean daily dose ug; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	46	44	-	MD 14 higher (75 lower to 103 higher)	⊕OOO VERY LOW	IMPORTANT

1 The majority of the evidence was from studies at very high risk of bias
2 95% CI crosses one MID
3 95% CI for the absolute effect crosses one MID
4 95% CI crosses both MIDs

Table 184: Clinical evidence profile: Adults and young people (>16 years) overall: Monitoring questionnaires + treatment vs UC + treatment.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adults overall: Monitoring control + treatment	UC + treatment	Relative (95% CI)	Absolute		
QOL (≥ 6months) (follow-up 6-12 months; measured with: AQLQ; range of scores: 1-7; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	171	162	-	MD 0.32 higher (0.17 to 0.47 higher)	⊕⊕⊕O MODERATE	CRITICAL
Exacerbations (≥ 6months) (follow-up 12 months; assessed with: course of OCS)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/91 (12.1%)	10.9%	HR 1.18 (0.51 to 2.73)	18 more per 1000 (from 52 fewer to 161 more)	⊕OOO VERY LOW	CRITICAL
Exacerbations (≥ 6months) (follow-up 6-12 months; assessed with: ER, hospitalisation or OCS)												
2	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[4]	none	21/171 (12.3%)	11.2%	RR 1.1 (0.61 to 1.99)	11 more per 1000 (from 44 fewer to 111 more)	⊕OOO VERY LOW	CRITICAL
UHU (≥ 6months) (follow-up 6 months; assessed with: ER or hospitalisation)												
1	randomised	very	no serious	no serious	serious[4]	none	1/80	7.1%	RR 0.17	59 fewer per 1000	⊕OOO	CRITICAL

	trials	serious[5]	inconsistency	indirectness			(1.3%)		(0.02 to 1.46)	(from 70 fewer to 33 more)	VERY LOW	
Asthma control (< 6months) (follow-up 3 months; measured with: ACT; range of scores: 5-25; Better indicated by higher values)												
1	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	99	84	-	MD 0.3 higher (0.73 lower to 1.33 higher)	⊕⊕OO LOW	CRITICAL
Asthma control (≥ 6months) (follow-up 12 months; measured with: ACQ ; range of scores: 0-6; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	91	92	-	MD 0.47 lower (0.64 to 0.3 lower)	⊕⊕OO LOW	CRITICAL
Asthma control (≥ 6months) (follow-up 6 months; measured with: ACT; range of scores: 5-25; Better indicated by higher values)												
1	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	80	70	-	MD 0.5 higher (0.86 lower to 1.86 higher)	⊕⊕OO LOW	CRITICAL
Lung function (≥ 6months) (follow-up 12 months; measured with: FEV1 L; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	91	92	-	MD 0.25 higher (0.03 to 0.47 higher)	⊕⊕OO LOW	IMPORTANT
Symptom free days (≥ 6months) (follow-up 12 months; measured with: % over 2 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	91	92	-	MD 10.9 higher (0.05 to 21.75 higher)	⊕⊕OO LOW	IMPORTANT
ICS use (≥ 6months) (follow-up 12 months; measured with: mean daily dose ug; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	91	92	-	MD 57 higher (38 lower to 152 higher)	⊕OOO VERY LOW	IMPORTANT
Rescue medication (< 6months) (follow-up 3 months; measured with: puffs/day; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	99	84	-	MD 0.62 lower (1.21 to 0.03 lower)	⊕⊕OO LOW	IMPORTANT
Rescue medication (> 6months) (follow-up 6 months; measured with: puffs/day; Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	80	70	-	MD 0.23 lower (0.66 lower to 0.2 higher)	⊕⊕⊕O MODERATE	IMPORTANT

1 The majority of the evidence was from studies at high risk of bias
2 95% CI crosses both the MIDs
3 Evidence from one study with an indirect outcome (ER, hospitalisation or OCS)
4 95% CI for the absolute effect crosses one MID
5 The majority of the evidence was from studies at very high risk of bias
6 95% CI crosses one MID

I.2 Monitoring: Lung function tests

Table 185: Clinical evidence profile: Adults: Monitoring PEF versus symptom monitoring

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PEF versus symptoms monitoring: adults	Control	Relative (95% CI)	Absolute		
QOL ≥6 months (follow-up 2 years; assessed with: AQLQ increase >0.5 points)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	52/134 (38.8%)	39.1%	RR 0.99 (0.73 to 1.35)	4 fewer per 1000 (from 106 fewer to 137 more)	⊕OOO VERY LOW	CRITICAL
QOL ≥6 months (follow-up 2 years; assessed with: AQLQ decrease >0.5 points)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	16/134 (11.9%)	8.6%	RR 1.39 (0.67 to 2.88)	34 more per 1000 (from 28 fewer to 162 more)	⊕OOO VERY LOW	CRITICAL
Exacerbation ≥6 months (follow-up 6-12 months; assessed with: need for OCS)												
2	randomised	very	serious[4]	no serious	very serious[3]	none	17/71	16.9%	RR 1.28 (0.29 to	47 more per 1000 (from 120 fewer to	⊕OOO	CRITICAL

	trials	serious[1]		indirectness			(23.9%)		5.57)	772 more)	VERY LOW	
Exacerbations ≥6 months (follow-up 12 months; measured with: number of OCS courses; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	45	-	MD 0.20 lower (0.74 lower to 0.34 higher)	⊕⊕OO LOW	CRITICAL
UHU ≥6 months (follow-up 2 years; measured with: Total asthma-related health care utilisation; Better indicated by lower values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	148	146	-	MD 0.11 lower (0.59 lower to 0.37 higher)	⊕⊕⊕O MODERATE	CRITICAL
UHU ≥6 months (follow-up 6-12 months; assessed with: Hospitalisation)												
3	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/146 (2.7%)	2.2%	RR 1.17 (0.31 to 4.43)	4 more per 1000 (from 15 fewer to 75 more)	⊕OOO VERY LOW	CRITICAL
UHU ≥6 months (follow-up 12 months; measured with: Number of hospital admissions; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	50	45	-	MD 0.05 lower (0.16 lower to 0.06 higher)	⊕OOO VERY LOW	CRITICAL
UHU ≥6 months (follow-up 12 months; measured with: days hospitalisation; Better indicated by lower values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	48	40	-	MD 0.03 lower (0.21 lower to 0.15 higher)	⊕⊕⊕O MODERATE	CRITICAL
UHU ≥6 months (follow-up 6-12 months; assessed with: ED visits)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	9/100 (9%)	2/92 (2.2%)	RR 3.78 (0.96 to 14.93)	60 more per 1000 (from 1 fewer to 303 more)	⊕OOO VERY LOW	CRITICAL
UHU ≥6 months (follow-up 12 months; measured with: Mean number of ED visits ; Better indicated by lower values)												
2	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	98	85	-	MD 0.04 lower (0.2 lower to 0.12 higher)	⊕⊕⊕O MODERATE	CRITICAL

UHU ≥6 months (follow-up 6 months; assessed with: Unscheduled doctors visit)												
2	randomised trials	serious[5]	very serious[6]	no serious indirectness	very serious[3]	none	22/90 (24.4%)	28.1%	RR 0.77 (0.18 to 3.34)	65 fewer per 1000 (from 230 fewer to 658 more)	⊕OOO VERY LOW	CRITICAL
Rescue medication ≥6months (follow-up 12 months; assessed with: requiring nebulised salbutamol)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/28 (10.7%)	5.4%	RR 1.98 (0.35 to 11.08)	53 more per 1000 (from 35 fewer to 544 more)	⊕OOO VERY LOW	IMPORTANT
FEV1 L ≥6 months (follow-up 12 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	48	40	-	MD 0.26 lower (0.61 lower to 0.09 higher)	⊕OOO VERY LOW	IMPORTANT
FEV1 % ≥6 months (follow-up 6-12 months; range of scores: 0-100; Better indicated by higher values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	87	76	-	MD 0.10 higher (0.92 lower to 1.12 higher)	⊕⊕OO LOW	IMPORTANT
PEF % best ≥6 months (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	31	32	-	MD 5.31 higher (1.91 lower to 12.53 higher)	⊕OOO VERY LOW	IMPORTANT
Time off school/work ≥6 months (follow-up 6-12 months)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	11/100 (11%)	8.3%	RR 1.41 (0.62 to 3.21)	34 more per 1000 (from 32 fewer to 183 more)	⊕OOO VERY LOW	IMPORTANT
Mean days off work ≥6 months (follow-up 12 months; Better indicated by lower values)												
2	randomised	very	no serious	no serious	serious[2]	none	98	85	-	MD 2.5 higher (1.27	⊕OOO	IMPORTANT

	trials	serious[1]	inconsistency	indirectness						to 3.74 higher)	VERY LOW	

[1] The majority of the evidence was from studies at very high risk of bias
[2] 95% CI crosses one MID
[3] 95% CI crosses two MIDs
[4] Heterogeneity in the point estimates, I2=52%
[5] The majority of the evidence was from studies at high risk of bias
[6] Heterogeneity in the point estimates, I2=86%

Table 186: Clinical evidence profile: Children: Monitoring PEF versus symptom monitoring

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PEF versus symptoms monitoring: children**	**Control**	**Relative (95% CI)**	**Absolute**		
Exacerbations <6months (follow-up 3 months; assessed with: OCS)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/12 (8.3%)	8.3%	RR 1.00 (0.07 to 14.21)	0 fewer per 1000 (from 77 fewer to 1000 more)[3]	⊕OOO VERY LOW	CRITICAL
Exacerbations ≥6months (follow-up 12 months; assessed with: OCS)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/19 (36.8%)	0%	OR 16.34 (3.25 to 82.24)	370 more per 1000 (from 150 more to 590 more)[3]	⊕⊕OO LOW	CRITICAL
UHU <6 months (follow-up 12 weeks; assessed with: Hospitalisation)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/44 (2.3%)	0%	OR 7.56 (0.15 to 381.04)	20 more per 1000 (from 40 fewer to 80 more)[3]	⊕OOO VERY LOW	CRITICAL
UHU <6 months (follow-up 12 weeks; assessed with: Attendance at A&E)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/44 (2.3%)	0%	OR 7.56 (0.15 to 381.04)	20 more per 1000 (from 40 fewer to 80 more)[3]	⊕OOO VERY LOW	CRITICAL

UHU(<6 months) (follow-up 12 weeks; assessed with: Emergency GP visits)											
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/44 (22.7%)	24.4%	RR 0.93 (0.44 to 1.97)	17 fewer per 1000 (from 137 fewer to 237 more)	⊕OOO VERY LOW	CRITICAL
Rescue meds ≥6 months (follow-up 12 months; assessed with: requiring nebulised salbutamol)											
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	2/17 (11.8%)	0%	OR 14.15 (0.79 to 252.1)	120 more per 1000 (from 50 fewer to 280 more)[3]	⊕OOO VERY LOW	IMPORTANT
FEV1 % best (<6 months) (follow-up 12 weeks; Better indicated by higher values)											
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	101	101	-	MD 0.39 higher (0.21 lower to 0.98 higher)	⊕⊕OO LOW	IMPORTANT
PEF % best (<6 months) (follow-up 12 weeks; Better indicated by higher values)											
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	44	45	-	MD 2.8 higher (2.15 to 3.45 higher)	⊕OOO VERY LOW	IMPORTANT
Time off school (<6 months) (follow-up 12 weeks)											
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	15/44 (34.1%)	28.9%	RR 1.18 (0.64 to 2.18)	52 more per 1000 (from 104 fewer to 341 more)	⊕OOO VERY LOW	IMPORTANT

[1] The majority of the evidence was from studies at very high risk of bias
[2] 95% CI crosses 2 MIDs
[3] Manual risk difference calculation due to no events in one group
[4] The majority of the evidence was from studies at high risk of bias
[5] 95% CI crosses one MID

I.3 Monitoring: FeNO

Table 187: Clinical evidence profile: FeNO versus Conventional Monitoring Adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FeNO versus conventional monitoring ADULTS	Control	Relative (95% CI)	Absolute		
UHU (ED visit) ≥6 months (follow-up mean 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/205 (0.98%)	1.4%	OR 0.68 (0.12 to 3.98)	4 fewer per 1000 (from 12 fewer to 39 more)	⊕OOO VERY LOW	CRITICAL
UHU (hospitalisation) ≥6 months (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/205 (0.49%)	1%	OR 0.52 (0.05 to 5.07)	5 fewer per 1000 (from 9 fewer to 39 more)	⊕OOO VERY LOW	CRITICAL
Exacerbation (OCS) ≥6 months (follow-up mean 52 weeks)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	33/197 (16.8%)	31.3%	RR 0.84 (0.56 to 1.26)	50 fewer per 1000 (from 138 fewer to 81 more)	⊕OOO VERY LOW	CRITICAL
Exacerbation (OCS) ≥6 months (follow-up mean 9 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	-	-	HR 0.91 (0.39 to 2.11)	-[3]	⊕OOO VERY LOW	CRITICAL
Exacerbation (OCS) ≥6 months (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	-	-	OR 0.64 (0.27 to 1.56)	-[3]	⊕OOO VERY LOW	CRITICAL

Exacerbation (mixed) <6 months (follow-up mean 4-6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	Serious indirectness[6]	Serious imprecision[2]	none	28/111 (25.2%)	41.3%	RR 0.61 (0.41 to 0.90)	161 fewer per 1000 (from 41 fewer to 244 fewer)	⊕⊕OO LOW	CRITICAL
AQLQ (≥ 6months) (follow-up mean 6 weeks; measured with: Asthma Quality of Life Questionnaire; range of scores: 1-7; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	115	112	-	MD 0 higher (0.22 lower to 22 higher)[5]	⊕⊕OO LOW	CRITICAL
ACQ ≥6 months (follow-up 9-12 months; measured with: Asthma Con1trol Questionnaire; range of scores: 0-6; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	320	324	-	MD 0.05 lower (0.13 lower to 0.04 higher)	⊕⊕⊕O MODERATE	CRITICAL
ACQ (clinically important improvement, ≥0.5) ≥6 months (follow-up mean 12 months; assessed with: Asthma Control Questionnaire)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29/81 (35.8%)	25.7%	RR 1.39 (0.86 to 2.26)	100 more per 1000 (from 36 fewer to 324 more)	⊕OOO VERY LOW	CRITICAL
ACQ (mean ACQ at exacerbation) <6 months (follow-up mean 4-6 months; assessed with: Asthma Control Questionnaire)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	111	109	-	MD 0.16 lower (0.36 lower to 0.04 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
ACQ (mean ACQ score at unscheduled doctor visit) <6 months (follow-up mean 4-6 months; assessed with: Asthma Control Questionnaire)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	111	109	-	MD 0.05 higher (0.18 lower to 0.28 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
ACQ (mean ACQ score overall) <6 months (follow-up mean 4-6months; assessed with: Asthma Control Questionnaire)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	111	109	-	MD 0.02 lower (0.21 lower to 0.25 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
FEV1 %pred (follow-up 9-12 months; range of scores: 0-100; Better indicated by higher values)												

3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	366	370	-	MD 0.45 higher (0.69 lower to 1.59 higher)	⊕OOO VERY LOW	IMPORTANT
FEV1, litres ≥6 months (follow-up mean 12 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	88	78	-	MD 0.03 lower (0.11 lower to 0.06 higher)	⊕⊕OO LOW	IMPORTANT
PEF am (L/min) ≥6 months (follow-up 9-12 months; Better indicated by higher values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	161	160	-	MD 2 higher (10.39 lower to 14.39 higher)	⊕⊕OO LOW	IMPORTANT
PEF pm (L/min) ≥6 months (follow-up mean 9 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	115	112	-	MD 3.8 higher (10 lower to 17.6 higher)	⊕⊕OO LOW	IMPORTANT
ICS use ≥6 months (follow-up mean 12 months; measured with: fluticasone or BDP equivalent; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	serious[6]	serious[2]	none	104	108	-	SMD 0.53 lower (0.8 to 0.25 lower)	⊕OOO VERY LOW	IMPORTANT
Rescue medication (puffs/day) ≥6 months (follow-up 9-12 months; Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	serious[6]	no serious imprecision	none	161	160	-	MD 0.06 lower (0.12 lower to 0 higher)	⊕OOO VERY LOW	IMPORTANT
% symptom free days ≥6 months (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	46	48	-	MD 5.6 higher (8.51 lower to 19.71 higher)	⊕OOO VERY LOW	IMPORTANT
Time of work (number of people) ≥6 months (follow-up 9 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	-	-	OR 2 (1.17 to 3.41)	-[3]	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by one increment if the majority of the evidence was at high risk of bias, and downgraded by two increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by one increment if the confidence interval crossed one MID or by two increments if the confidence interval crossed both MIDs
[3] Control group event rate not reported
[5] 97.5% CI reported and extracted
[6] Downgraded by one/two increments because: the majority of the evidence had indirect outcomes

Table 188: Clinical evidence profile: FeNO versus Conventional Monitoring Children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FeNO versus conventional monitoring CHILD	Control	Relative (95% CI)	Absolute		
UHU (unscheduled visits) ≥6 months (follow-up 46-52 weeks)												
2	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	very serious[2]	none	65/294 (22.1%)	29.9%	RR 0.67 (0.29 to 1.55)	99 fewer per 1000 (from 212 fewer to 164 more)	⊕OOO VERY LOW	CRITICAL
UHU (hospitalisation) ≥6 months (follow-up 46-52 weeks)												
4	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	15/366 (4.1%)	3.4%	RR 0.97 (0.48 to 1.95)	1 fewer per 1000 (from 18 fewer to 32 more)	⊕OOO VERY LOW	CRITICAL
UHU (number of children ≥1 emergency room admin) ≥6 months (follow-up mean 52 weeks)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/45 (4.4%)	8.7%	RR 0.51 (0.1 to 2.65)	43 fewer per 1000 (from 78 fewer to 144 more)	⊕OOO VERY LOW	CRITICAL
Exacerbation (OCS) ≥6 months (follow-up mean 43 weeks)												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	115/462 (24.9%)	19.2%	RR 0.74 (0.61 to 0.9)	50 fewer per 1000 (from 19 fewer to 75 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Asthma control (ACT score) ≥6 months (follow-up mean 46 weeks; measured with: ACT; range of scores: 5-25; Better indicated by higher values)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	250	244	-	MD 0.06 higher (0.27 lower to 0.39 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
PACQLQ (Pediatric Asthma Caregiver) ≥6 months (follow-up mean 30 weeks; measured with: Pediatric Asthma Care Quality of Life Questionnaire; range of scores: 1-7; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	75	72	-	MD 0 higher (0.24 lower to 0.24 higher)	⊕⊕OO LOW	CRITICAL
FEV1 % pred ≥6 months (follow-up 46-52 weeks; range of scores: 0-100; Better indicated by higher values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	289	290	-	MD 0.94 higher (0.31 lower to 2.19 higher)	⊕⊕⊕O MODERATE	IMPORTANT
ICS dose ≥6 months (follow-up 46 weeks; measured with: fluticasone; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[4]	no serious imprecision	none	250	244	-	MD 118.9 higher (48.5 to 189.3 higher)	⊕⊕⊕O MODERATE	IMPORTANT
% symptom free days ≥6 months (follow-up 30 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	75	72	-	MD 0.3 higher (10 lower to 10.6 higher)	⊕OOO VERY LOW	IMPORTANT
Number of symptom days in last 2 weeks; ≥6 months (follow-up mean 46 weeks; Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	250	244	-	MD 0.04 higher (0.21 lower to 0.29 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Number of patients not using inhaled corticosteroids or anti-leukotrienes ≥6 months (follow-up mean 12 months)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/32 (6.3%)	18.8%	RR 0.33 (0.07 to 1.53)	126 fewer per 1000 (from 175 fewer to 100 more)	⊕OOO VERY LOW	IMPORTANT
Rescue medication (no. of patients needed beta-agonist due to symptoms) ≥6 months (follow-up mean 12 months)												
1	randomised	very	no serious	no serious	serious[2]	none	16/32	81.3%	RR 0.62	309 fewer per 1000	⊕OOO	IMPORTANT

	trials	serious[3]	inconsistency	indirectness			(50%)		(0.42 to 0.9)	(from 81 fewer to 472 fewer)	VERY LOW	
Number of school days missed in last 2 weeks; ≥6 months (follow-up mean 46 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	250	244	-	MD 0.04 lower (0.12 lower to 0.04 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Time off (school/work - number of children missed school) ≥6 months (follow-up mean 12 months)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/46 (21.7%)	26.1%	RR 0.83 (0.4 to 1.73)	44 fewer per 1000 (from 157 fewer to 191 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by one/two increments because: heterogeneity, I2=50%, p=0.04
[2] Downgraded by one increment if the confidence interval crossed one MID or by two increments if the confidence interval crossed both MIDs
[3] Downgraded by one increment if the majority of the evidence was at high risk of bias, and downgraded by two increments if the majority of the evidence was at very high risk of bias
[4] Downgraded by one/two increments because: the majority of the evidence had indirect outcomes

I.4 Monitoring: Challenge tests

Table 189: Clinical evidence summary: ADULTS Methacholine challenge test versus no challenge test for asthma monitoring

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ADULTS Methacholine challenge test versus no challenge test**	**Control**	**Relative (95% CI)**	**Absolute**		
Mortality (≥6 months) (follow-up 40 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/105 (0.95%)	0%	OR 7.53 (0.15 to 379.61)	10 more per 1000 (from 20 fewer to 40 more)[3]	⊕OOO VERY LOW	CRITICAL
Asthma exacerbations (≥6 months) (follow-up 40 weeks)												

1	randomised trials	very serious[1]	no serious inconsistency	serious[4]	very serious[2]	none	22/105 (21%)	24.3%	RR 0.86 (0.52 to 1.42)	34 fewer per 1000 (from 117 fewer to 102 more)	⊕OOO VERY LOW	CRITICAL
Rescue medications (≥6 months) (follow-up 40 weeks; measured with: Albuterol puffs/day; Better indicated by lower values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	105	107	-	MD 0.1 lower (0.58 lower to 0.38 higher)	⊕⊕⊕O MODERATE	IMPORTANT
ICS use >6months (follow-up 40 weeks; measured with: mean daily dose (mcg; fluticasone propionate); Better indicated by higher values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	105	107	-	MD 131.2 higher (83.57 to 178.83 higher)	⊕⊕⊕O MODERATE	IMPORTANT
FEV1 (≥6 months) (follow-up 40-104 weeks; measured with: L; Better indicated by higher values)												
2	randomised trials	serious[5]	serious[6]	no serious indirectness	no serious imprecision	none	137	142	-	MD 0.04 lower (0.09 lower to 0.16 higher)	⊕⊕OO LOW	IMPORTANT
% symptom free days (≥6 months) (follow-up 40 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	105	107	-	MD 5.1 lower (20.06 lower to 9.86 higher)	⊕⊕⊕O MODERATE	IMPORTANT
PEF am (≥6 months) (follow-up 40 weeks; measured with: L/min; Better indicated by higher values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	105	107	-	MD 8.6 lower (17.20 lower to 0 higher)	⊕⊕⊕O MODERATE	IMPORTANT
PEF pm (≥6 months) (follow-up 40 weeks; measured with: L/min; Better indicated by higher values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[7]	none	105	107	-	MD 6 lower (29.96 lower to 17.96 higher)	⊕⊕OO LOW	IMPORTANT

[1] The majority of the evidence was from studies at very high risk of bias due to allocation concealment and missing data
[2] 95% CI crosses 2 MIDs
[3] Manual calculation of absolute effect as zero events in the control group
[4] Evidence from one study - exacerbations not defined
[5] The majority of the evidence was from studies at high risk of bias due to allocation concealment
[6] Point estimates show statistical heterogeneity I2=72% P<0.06. Only 2 studies so random effects model used.
[7] 95% CI crosses one MID

Table 190: Clinical evidence summary: ADULTS Mannitol challenge test versus no challenge test for asthma monitoring

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ADULTS Mannitol challenge test versus no challenge test	Control	Relative (95% CI)	Absolute		
AQLQ (≥6 months) (follow-up 52 weeks; measured with: mini AQLQ; range of scores: 1-7; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	61	58	-	MD 0.06 higher (0.3 lower to 0.42 higher)	⊕⊕OO LOW	CRITICAL
Asthma exacerbations (≥6 months) (follow-up 52 weeks)												
1	randomised trials	serious[3]	no serious inconsistency	serious[2]	very serious[4]	none	12/61 (19.7%)	22.4%	RR 0.88 (0.44 to 1.76)	27 fewer per 1000 (from 125 fewer to 170 more)	⊕OOO VERY LOW	CRITICAL
Rescue medications (≥6 months) (follow-up 52 weeks; measured with: Albuterol puffs/day; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[5]	none	61	58	-	MD 0.31 lower (0.73 lower to 0.11 higher)	⊕OOO VERY LOW	IMPORTANT
ICS use >6months (follow-up 52 weeks; measured with: mean daily dose (mcg; ciclesonide); Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	61	58	-	MD 306 higher (241.71 to 370.29	⊕⊕OO LOW	IMPORTANT

										higher)		
FEV1% (≥6 months) (follow-up 52 weeks; Better indicated by higher values)												
1	randomised trials	serious[1,6]	no serious inconsistency	serious[2]	no serious imprecision	none	61	58	-	MD 0.3 higher (8.21 lower to 8.81 higher)	⊕⊕OO LOW	IMPORTANT
PEF% (≥6 months) (follow-up 52 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	61	58	-	MD 2.7 lower (13.17 lower to 7.77 higher)	⊕⊕OO LOW	IMPORTANT
PEF am (≥6 months) (follow-up 52 weeks; measured with: L/min; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[4]	none	61	58	-	MD 1.5 higher (34.7 lower to 37.7 higher)	⊕OOO VERY LOW	IMPORTANT

[1] The majority of the evidence was from studies at high risk of bias due to blinding
[2] Patients initially underwent step-down of their existing treatment. Patients on combination inhalers were switched to an equivalent dose of the same ICS only (unclear whether LABA was continued).
[3] The majority of the evidence was from studies at high risk of bias due to missing data
[4] 95% CI crosses 2 MIDs
[5] 95% CI crosses one MID
[6] The majority of the evidence was from studies at high risk of bias due to baseline differences

Table 191: Clinical evidence profile: CHILDREN Challenge test versus no challenge test for asthma monitoring

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CHILDREN Challenge test versus no challenge test**	**Control**	**Relative (95% CI)**	**Absolute**		
Asthma exacerbations (≥6 months) (follow-up 2 years; assessed with: OCS course)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	16/102 (15.7%)	16.4%	RR 0.96 (0.51 to	7 fewer per 1000 (from 80 fewer to 130	⊕OOO VERY	CRITICAL

									1.79)	more)	LOW	
ICS dose (follow-up 2 years; measured with: Mean daily dose for treatment period; Better indicated by higher values)												
1	randomised trials	serious[4]	no serious inconsistency	serious[2]	serious[5]	none	85	90	-	MD 84 higher (10.66 to 157.34 higher)	⊕OOO VERY LOW	IMPORTANT
FEV1% (≥6 months) (follow-up 2 years; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[4]	no serious inconsistency	serious[2]	no serious imprecision	none	93	92	-	MD 6 higher (1.2 lower to 10.8 higher)	⊕⊕OO LOW	IMPORTANT
% symptom free days (≥6 months) (follow-up 2 years; measured with: in last 3 months of treatment; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[4]	no serious inconsistency	serious[2]	very serious[3]	none	85	90	-	MD 1.1 lower (10.1 lower to 7.9 higher)	⊕OOO VERY LOW	IMPORTANT

[1] No explanation was provided
[2] Patients initially underwent step-down of their existing treatment.
[3] 95% CI crosses both MIDs
[4] The majority of the evidence was at high risk of bias due to allocation concealment and baseline differences
[5] 95% CI crosses one MID

I.5 Monitoring adherence to treatment

Table 192: Clinical evidence profile: Children with uncontrolled asthma: Monitoring adherence + treatment vs UC + treatment for asthma

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Children with uncontrolled asthma: Monitoring adherence + treatment**	**UC + treatment**	**Relative (95% CI)**	**Absolute**		
Adherence <6months (follow-up 4 months; measured with: % of prescribed doses measured by the electronic inhaler; Better indicated by higher values)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14	12	-	MD 28.9 higher (8.62 to 49.18 higher)	⊕OOO VERY LOW	CRITICAL
Adherence ≥6months (follow-up 18 months; measured with: Number of canister refills (100% adherence = 3.0); range of scores: 0-3; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	76	81	-	MD 0.02 lower (0.29 lower to 0.25 higher)	⊕⊕OO LOW	CRITICAL
Adherence (self-reported) ≥6months (follow-up 18 months; measured with: % self-reported adherence in previous 6 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	76	81	-	MD 1.95 higher (5.87 lower to 9.77 higher)	⊕⊕OO LOW	CRITICAL
Exacerbation < 6months (follow-up 4 months; assessed with: need for OCS)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/14 (21.4%)	8.3%	RR 2.57 (0.31 to 21.59)	130 more per 1000 (from 57 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Exacerbation ≥6 months (follow-up 18 months; measured with: no. of OCS courses in 6 months; Better indicated by lower values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	76	81	-	MD 0.22 higher (0.19 lower to 0.63 higher)	⊕⊕⊕O MODERATE	CRITICAL
UHU ≥6 months (follow-up 18 months; measured with: Hospitalisations in previous 6 months ; Better indicated by lower values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	76	81	-	MD 0 higher (4.8 lower to 4.8 higher)	⊕⊕⊕O MODERATE	CRITICAL
Rescue medication < 6months (follow-up 4 months; assessed with: Reliever medication 3 or more times a week)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/14 (14.3%)	0%	OR 6.92 (0.41 to	140 more per 1000 (from 7 more to 360	⊕OOO VERY LOW	IMPORTANT

									118.14)	more)[5]		

[1] The majority of the evidence was from studies at very high risk of bias
[2] 95% CI crosses one MID
[3] 95% CI crosses both MIDs
[4] The majority of the evidence was from studies at high risk of bias
[5] Manual calculation of absolute risk difference as no events in the control group

Table 193: Clinical evidence profile: Adults overall: Monitoring adherence + treatment vs UC + treatment for asthma

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adults overall: Monitoring adherence + treatment	UC + treatment	Relative (95% CI)	Absolute		
Adherence ≥6months (follow-up 12 months; measured with: % adherence to prescription refills in previous 3 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0	-	-	MD 2 lower (8.61 lower to 4.61 higher)	⊕OOO VERY LOW	CRITICAL
QOL <6months (follow-up 10 weeks; measured with: AQLQ; range of scores: 1-7; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	serious[4]	serious[5]	none	10	9	-	MD 0.37 higher (0.08 to 0.66 higher)	⊕OOO VERY LOW	CRITICAL
Exacerbation ≥6months (follow-up 12 months; assessed with: course of OCS)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	307/1335 (23%)	22%	HR 1.07 (0.89 to 1.29)	13 more per 1000 (from 22 fewer to 54 more)	⊕⊕OO LOW	CRITICAL
UHU (hospitalisation) ≥6months (follow-up 12 months)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	10/1335 (0.75%)	0.81%	HR 0.86 (0.32 to 2.31)	1 fewer per 1000 (from 6 fewer to 11 more)	⊕OOO VERY LOW	CRITICAL
UHU (ED visit) ≥6months (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	127/1335 (9.5%)	8.1%	HR 1.22 (0.83 to 1.79)	17 more per 1000 (from 13 fewer to 59 more)	⊕OOO VERY LOW	CRITICAL
Lung function <6months (follow-up 10 weeks; measured with: FEV1 L; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	serious[4]	very serious[2]	none	10	9	-	MD 0.12 lower (7.31 lower to 7.07 higher)	⊕OOO VERY LOW	IMPORTANT

1 The majority of the evidence was from studies at very high risk of bias
2 95% CI crosses both MIDs
3 The majority of the evidence is from studies at very high risk of bias
4 Population indirectness: includes severe asthma
5 95% CI crosses one MID
6 95% CI crosses both the MIDs but only downgraded by one as the 95% CI for the absolute effect is small

I.6 Monitoring inhaler technique

Table 194: ADULTS: Monitoring inhaler technique vs no monitoring for asthma

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ADULTS: Monitoring inhaler technique**	**No monitoring**	**Relative (95% CI)**	**Absolute**		
Lung function <6 months (follow-up 3 months; measured with: PEF Min%Max (higher is less variability); range of scores: 0-100; Better indicated by higher values)												
1	randomised	very	no serious	no serious	serious[2]	none	53	44	-	MD 6.2 higher (2.68 to 9.72	⊕OOO VERY	IMPORTANT

	trials	serious[1]	inconsistency	indirectness						higher)	LOW	
Lung function ≥6 months (follow-up 6 months; measured with: PEF Min%Max (higher is less variability); range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	53	44	-	MD 4.5 higher (0.79 to 8.21 higher)	⊕OOO VERY LOW	IMPORTANT
QOL <6 months (follow-up 3 months; measured with: Marks AQLQ; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	53	44	-	MD 0.55 lower (0.77 to 0.33 lower)	⊕⊕OO LOW	CRITICAL
QOL ≥6 months (follow-up 6 months; measured with: Marks AQLQ; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	53	44	-	MD 0.5 lower (0.74 to 0.26 lower)	⊕OOO VERY LOW	CRITICAL

[1] The evidence was from one study at very high risk of bias for this outcome
[2] 95% CI crosses one MID

Table 195: ADULTS: Monitoring (verbal and electronic) vs verbal monitoring only for asthma

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ADULTS: Monitoring (verbal and electronic)**	**Verbal monitoring only**	**Relative (95% CI)**	**Absolute**		
QOL <6 months (follow-up 6 weeks; measured with: mini AQLQ; range of scores: 1-7; Better indicated by higher values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	53	52	-	MD 0.38 higher (0.02 lower to 0.79 higher)	⊕OOO VERY LOW	CRITICAL

Lung function <6 months (follow-up 6 weeks; measured with: FEV1 L; Better indicated by higher values)											
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	36	35	-	MD 0.23 lower (0.55 lower to 0.09 higher)	⊕OOO VERY LOW	IMPORTANT
Lung function <6 months (follow-up 6 weeks; measured with: FEV1 % pred; range of scores: 0-100; Better indicated by higher values)											
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	17	17	-	MD 9.1 higher (3.71 lower to 21.91 higher)	⊕⊕OO LOW	IMPORTANT

[1] The majority of the evidence was from studies at very high risk of bias for this outcome
[2] 95% CI crosses one MID
[3] The majority of the evidence was from studies at high risk of bias for this outcome

Table 196: CHILDREN: Monitoring (verbal and electronic) vs verbal monitoring only for asthma

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CHILDREN: Monitoring (verbal and electronic)**	**Verbal monitoring only**	**Relative (95% CI)**	**Absolute**		
Lung function <6 months (follow-up 6 weeks; measured with: FEV1 % pred; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6	6	-	MD 3.2 lower (15.27 lower to 8.87 higher)	⊕OOO VERY LOW	IMPORTANT
QOL <6 months (follow-up 6 weeks; measured with: PAQLQ; range of scores: 1-7; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	6	6	-	MD 0.03 higher (0.66 lower to 0.72 higher)	⊕OOO VERY LOW	CRITICAL

[1] The evidence was from one study at high risk of bias for this outcome
[2] 95% CI crosses both MIDs
[3] No explanation was provided

I.7 Monitoring: Tele-healthcare

Table 197: Adult comparison 1: tele-health services vs face-to-face equivalents

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tele-health services	face-to-face equivalents	Relative (95% CI)	Absolute		
Quality of life (follow-up mean 12 months; measured with: Asthma Quality of Life Questionnaire; range of scores: 1-7; Better indicated by higher values)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	491	469	-	MD 0.01 lower (0.17 lower to 0.14 higher)	⊕⊕⊕O MODERATE	CRITICAL
UHU hospitalisation (follow-up mean 6 months[2])												
2	randomised trials	very serious[1,3]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/222 (0%)	0.6%	OR 0.14 (0 to 7.06)[5]	5 fewer per 1000 (from 6 fewer to 35 more)	⊕OOO VERY LOW	CRITICAL
UHU ED visit (follow-up mean 6 months[2])												
2	randomised trials	very serious[1,3]	no serious inconsistency	no serious indirectness	very serious[4]	none	2/222 (0.9%)	0%	OR 7.75 (0.48 to 124.9)[5]	-	⊕OOO VERY LOW	CRITICAL
Exacerbations requiring oral steroids												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	5/137 (3.6%)	2.1%	RR 1.72 (0.42 to 7.04)	15 more per 1000 (from 12 fewer to 127 more)	⊕OOO VERY LOW	CRITICAL
Asthma control (follow-up mean 12 months; measured with: Asthma Control Questionnaire; range of scores: 0-6; Better indicated by lower values)												

2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	354	328	-	MD 0.11 lower (0.27 lower to 0.04 higher)	⊕⊕⊕O MODERATE	CRITICAL
UHU GP visits (follow-up mean 6 months[2])												
2	randomised trials	serious[1,6]	no serious inconsistency	no serious indirectness	serious[4]	none	30/222 (13.5%)	13.2%	RR 0.86 (0.56 to 1.32)	18 fewer per 1000 (from 58 fewer to 42 more)	⊕⊕OO LOW	CRITICAL
Change in FEV1 (mL) (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	very serious[1,3]	no serious inconsistency	no serious indirectness	serious[7]	none	85	88	-	MD 152 higher (54 to 250 higher)	⊕OOO VERY LOW	IMPORTANT
Withdrawal (follow-up 6-12 months)												
3	randomised trials	no serious risk of bias	serious[8]	no serious indirectness	very serious[4]	none	35/334 (10.5%)	12%	RR 0.78 (0.32 to 1.9)	26 fewer per 1000 (from 82 fewer to 108 more)	⊕OOO VERY LOW	IMPORTANT

[1] Studies could not use blinding to control for performance or detection bias
[2] Pinnock 2003 was a pragmatic trial of variable intervention duration, but did not contribute any events to the analysis
[3] Evidence of sub-optimal randomisation procedures and imputation of missing values, and selective reporting
[4] 95% CI crosses both the MIDs
[5] Very rare events - Peto odds ratio used
[6] While there were several issues with one of the studies in the analysis, it only accounted for 6.6% of the analysis weight.
[7] 95% CI crossed an MID
[8] Heterogeneity was high (I squared = 79%)

Table 198: Adult comparison 2: tele-monitoring vs paper-based monitoring

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tele-monitoring	Paper-based monitoring	Relative (95% CI)	Absolute		
Quality of life (follow-up 6-12 months; measured with: Asthma Quality of Life Questionnaire; range of scores: 1-7; Better indicated by higher values)												

2	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	188	196	-	MD 0.21 higher (0.09 lower to 0.5 higher)	⊕OOO VERY LOW	CRITICAL
UHU hospitalisation (follow-up 4-6 months)												
3	randomised trials	serious[4]	serious[5]	no serious indirectness	very serious[6]	none	5/191 (2.6%)	2.2%	RR 0.60 (0.13 to 2.86)	9 fewer per 1000 (from 19 fewer to 41 more)	⊕OOO VERY LOW	CRITICAL
UHU ED visit (follow-up mean 6 months)												
2	randomised trials	serious[7]	serious[8]	no serious indirectness	very serious[6]	none	5/183 (2.7%)	13%	RR 0.89 (0.02 to 33.53)	14 fewer per 1000 (from 127 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Exacerbations requiring oral steroids (follow-up mean 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	28/140 (20%)	21.3%	RR 0.94 (0.59 to 1.49)	13 fewer per 1000 (from 87 fewer to 104 more)	⊕⊕OO LOW	CRITICAL
Asthma control (follow-up 6-12 months; measured with: Asthma Control Questionnaire; range of scores: 0-6; Better indicated by lower values)												
2	randomised trials	serious[1]	very serious[9]	no serious indirectness	serious[3]	none	240	238	-	MD 0.24 lower (0.72 lower to 0.24 higher)	⊕OOO VERY LOW	CRITICAL
UHU GP visits (follow-up mean 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	51/140 (36.4%)	29.1%	RR 1.25 (0.89 to 1.76)	73 more per 1000 (from 32 fewer to 221 more)	⊕⊕⊕O MODERATE	CRITICAL
Change in FEV1 (mL) (follow-up mean 12 months; Better indicated by higher values)												
1	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	serious[3]	none	101	99	-	MD 250 higher (33.36 to 466.64 higher)	⊕⊕OO LOW	IMPORTANT
PEF (L/min) (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[3]	none	43	46	-	MD 39.2 higher (16.58 to 61.82 higher)	⊕⊕OO LOW	IMPORTANT

Withdrawal (follow-up 4-12 months)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	58/312 (18.6%)	15.2%	RR 1.01 (0.73 to 1.39)	2 more per 1000 (from 41 fewer to 59 more)	⊕⊕OO LOW	IMPORTANT

[1] One study analysed complete cases and did not blind participants, investigators or outcome assessors, which carried the majority of the analysis weight.
[2] Heterogeneity was high (I squared = 53%)
[3] 95% CI crosses one of the MIDs
[4] Only one study used any blinding procedures (outcome assessors), and there were uncertainties regarding allocation concealment
[5] Heterogeneity was not statistically significant (I squared = 42%), but point estimates are very different
[6] 95% CIs cross both MIDs
[7] Study carrying the most weight did not blind outcome assessors (and could not blind participants and investigators), and dropout was high in both groups
[8] Heterogeneity was high (I squared = 80%)
[9] Heterogeneity was very high (I squared = 91%)
[10] No blinding of outcome assessors (and unable to blind participants and investigators). Only complete cases were analysed.

Table 199: Adult comparison 3: tele-healthcare package vs nothing (usual care)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Tele-health packages**	**Nothing (usual care)**	**Relative (95% CI)**	**Absolute**		
Quality of life (follow-up 10-12 months; measured with: Asthma Quality of Life Questionnaire; range of scores: 1-7; Better indicated by higher values)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	806	827	-	MD 0.08 higher (0.03 lower to 0.20 higher)	⊕⊕⊕O MODERATE	CRITICAL
UHU hospitalisation (follow-up 6-12 months)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	1/205 (0.49%)	5.6%	OR 0.16 (0.05 to 0.56)[4]	47 fewer per 1000 (from 24 fewer to 53 fewer)	⊕⊕⊕O MODERATE	CRITICAL
UHU ED visit (follow-up 6-12 months)												
4	randomised trials	serious[1]	no serious inconsistency[4]	no serious indirectness	very serious[5]	none	10/210 (4.8%)	6.5%	RR 0.82 (0.38 to 1.8)	12 fewer per 1000 (from 40 fewer to 52	⊕OOO VERY LOW	CRITICAL

										more)		
Exacerbations requiring oral steroids (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	21/31 (67.7%)	72.4%	RR 0.94 (0.67 to 1.3)	43 fewer per 1000 (from 239 fewer to 217 more)	⊕OOO VERY LOW	CRITICAL
Asthma control (follow-up mean 12 months; measured with: Asthma Control Questionnaire; range of scores: 0-6; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	270	286	-	MD 0.04 lower (0.2 lower to 0.12 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
UHU GP visits (follow-up 6-12 months)												
3	randomised trials	serious[1]	Serious[6]	no serious indirectness[7]	very serious[5]	none	31/150 (20.7%)	38.9%	RR 0.96 (0.39 to 2.37)	16 fewer per 1000 (from 237 fewer to 533 more)	⊕OOO VERY LOW	CRITICAL
Change in FEV1 (mL) (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[8]	none	85	80	-	MD 183 higher (85 to 281 higher)	⊕⊕OO LOW	IMPORTANT
Symptom days per month (range of scores: 0-30; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[8]	none	311	297	-	MD 0.6 higher (0.82 lower to 2.02 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Symptom nights per month (range of scores: 0-30; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[8]	none	311	297	-	MD 0.1 lower (1.21 lower to 1.01 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Withdrawal (follow-up 6-12 months)												
5	randomised trials	serious[1]	no serious inconsistency[(4)]	no serious indirectness	serious[5]	none	28/255 (11%)	11.1%	RR 0.81 (0.51 to 1.29)	21 fewer per 1000 (from 54 fewer to 32 more)	⊕OOO VERY LOW	IMPORTANT

[1] Issues across studies with blinding, completeness of outcome data, and allocation concealment
[2] Confidence intervals were wide but did not cross an MID
[3] Very rare events - Peto odds ratio used
[4] Point estimates were varied but statistical heterogeneity was low - random effects sensitivity did not change imprecision

[5] 95% CI crossed both MIDs
[6] Heterogeneity was high (I squared = 66%)
[7] One study was only recruited older adults (53% of analysis weight)
[8] 95% CIs crossed an MID

Table 200: Child comparison 1: tele-health services vs face-to-face equivalents

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tele-health services	face-to-face equivalents	Relative (95% CI)	Absolute		
Quality of life - child (follow-up mean 12 months; measured with: Paediatric Asthma Quality of Life Questionnaire; range of scores: 1-7; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	60	60	-	MD 0.3 higher (0.11 lower to 0.71 higher)	⊕⊕OO LOW	CRITICAL
Quality of life - caregiver (follow-up mean 12 months; measured with: Paediatric Asthma Quality of Life Questionnaire; range of scores: 1-7; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	60	60	-	MD 0.2 higher (0.12 lower to 0.52 higher)	⊕⊕OO LOW	CRITICAL
UHU hospitalisation (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	1/60 (1.7%)	1.7%	RR 1 (0.06 to 15.62)	0 fewer per 1000 (from 16 fewer to 249 more)	⊕OOO VERY LOW	CRITICAL
UHU ED visit (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/60 (6.7%)	3.3%	RR 2 (0.38 to 10.51)	33 more per 1000 (from 20 fewer to 314 more)	⊕OOO VERY LOW	CRITICAL
FEV1 % predicted (follow-up mean 12 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	60	60	-	MD 5.2 higher (1.48 lower to 11.88 higher)	⊕⊕OO LOW	IMPORTANT

[1] No blinding and unbalanced attrition
[2] 95% CI crosses an MID
[3] 95% CI crosses both MIDs

Table 201: Child comparison 2: tele-monitoring vs paper-based monitoring

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tele-monitoring	Paper-based monitoring	Relative (95% CI)	Absolute		
Change in morning PEF (L/min) (follow-up mean 3 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	82	71	-	MD 7.80 higher (6.37 lower to 21.97 higher)	⊕⊕OO LOW	IMPORTANT
Change in evening PEF (L/min) (follow-up mean 3 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	82	71	-	MD 12 higher (3.59 lower to 27.59 higher)	⊕⊕OO LOW	IMPORTANT
Withdrawal (follow-up mean 3 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/88 (6.8%)	6.6%	RR 1.04 (0.33 to 3.26)	3 more per 1000 (from 44 fewer to 149 more)	⊕OOO VERY LOW	IMPORTANT

[1] Participants and investigators could not be blind (outcome assessors were blinded)
[2] 95% CI crosses an MID
[3] 95% CI crosses both MIDs

Table 202: Child comparison 3: tele-healthcare package vs nothing (usual care)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tele-health packages	Nothing (usual care)	Relative (95% CI)	Absolute		

Quality of life - child (follow-up 6-12 months; measured with: Paediatric Asthma Quality of Life Questionnaire; range of scores: 1-7; Better indicated by higher values)												
1	randomised trials	serious[1]	No serious inconsistency	no serious indirectness	serious[3]	none	41	41	-	MD 0.70 higher (0.29 to 1.11 higher)	⊕⊕OO LOW	CRITICAL
Quality of life - caregiver (follow-up 6-12 months; measured with: Paediatric Asthma Quality of Life Questionnaire; range of scores: 1-7; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	89	92	-	MD 0.18 higher (0.10 lower to 0.46 higher)	⊕⊕⊕O MODERATE	CRITICAL
UHU hospitalisation (follow-up 3-12 months)												
5	randomised trials	serious[4]	no serious inconsistency[5]	no serious indirectness	very serious[6]	none	11/305 (3.6%)	2%	RR 1.43 (0.59 to 3.46)	9 more per 1000 (from 8 fewer to 49 more)	⊕OOO VERY LOW	CRITICAL
UHU ED visit (follow-up 3-12 months)												
4	randomised trials	serious[4]	no serious inconsistency[5]	no serious indirectness	very serious[6]	none	19/285 (6.7%)	9.2%	RR 1 (0.56 to 1.8)	0 fewer per 1000 (from 40 fewer to 74 more)	⊕OOO VERY LOW	CRITICAL
Exacerbations requiring oral steroids (follow-up 6-12 months)												
2	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[6]	none	41/62 (66.1%)	71.9%	RR 1.01 (0.8 to 1.27)	7 more per 1000 (from 144 fewer to 194 more)	⊕OOO VERY LOW	CRITICAL
Asthma control (follow-up mean 12 months; measured with: Asthma Control Questionnaire; range of scores: 0-6; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	148	153	-	MD 0.31 lower (0.56 to 0.06 lower)	⊕⊕OO LOW	CRITICAL
UHU GP visits (follow-up mean 8 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	6/48 (12.5%)	15.7%	RR 0.80 (0.30 to 2.13)	31 fewer per 1000 (from 110 fewer to 177 more)	⊕⊕OO LOW	CRITICAL
Withdrawal (follow-up 3-12 months)												
5	randomised	serious[4]	serious[7]	no serious	serious[6]	none	51/408	16.1%	RR 0.86	23 fewer per 1000	⊕OOO	IMPORTANT

	trials			indirectness			(12.5%)		(0.53 to 1.41)	(from 76 fewer to 66 more)	VERY LOW	

[1] One or more study did not blind outcome assessors
[2] MID is close to, but does not cross, the 0.5 MID
[3] 95% CI crosses one MID
[4] Issues across studies with blinding, completeness of outcome data, and allocation concealment
[5] Point estimates were varied but statistical heterogeneity was low - random effects sensitivity did not change imprecision
[6] 95% CI crosses both MIDs
[7] Some inconsistency (I squared = 38%), random effects used

Table 203: Adult comparison 4: Telehealthcare without healthcare professional involvement vs usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Interactive voice response telephone calls**	**no calls**	**Relative (95% CI)**	**Absolute**		
QOL <6 months (follow-up 10 weeks; measured with: AQLQ; range of scores: 0-7; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25	25	-	MD 0.23 higher (0.32 lower to 0.78 higher)	⊕⊕OO LOW	CRITICAL
Asthma Control Questionnaire <6 months (follow-up 10 weeks; measured with: ACT; range of scores: 5-25; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	25	25	-	MD 0.72 higher (1.51 lower to 2.95 higher)	⊕OOO VERY LOW	CRITICAL

[1] Method of randomisation and allocation concealment unclear
[2] Crosses one MID
[3] Crosses two MIDs

Table 204: Child comparison 4: Telehealthcare without healthcare professional involvement vs usual care

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Telephone calls**	**No calls**	**Relative (95% CI)**	**Absolute**		
Exacerbations ≥6 months (follow-up 6 months; assessed with: Self report OCS (assumed to be for exacerbation))												
1	randomised trials	very serious[1,2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	16/39 (41%)	52.5%	RR 0.78 (0.48 to 1.26)	116 fewer per 1000 (from 273 fewer to 136 more)	⊕OOO VERY LOW	CRITICAL
QOL ≥6 months (follow-up 6 months; measured with: Pediatric Asthma Quality of Life Questionnaire (carer); range of scores: 0-7; Better indicated by higher values)												
1	randomised trials	very serious[1,2,3]	no serious inconsistency	no serious indirectness	serious[4]	none	39	41	-	MD 0.2 higher (0.48 lower to 0.88 higher)	⊕OOO VERY LOW	CRITICAL
QOL ≥6 months (follow-up 6 months; measured with: Pediatric Asthma Quality of Life Questionnaire (child); range of scores: 0-7; Better indicated by higher values)												
1	randomised trials	very serious[1,2,3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	39	41	-	MD 0.6 higher (0.16 to 1.04 higher)	⊕⊕OO LOW	CRITICAL
UHU ED visit ≥6 months (follow-up 6 months; assessed with: ED visit self report)												
1	randomised trials	very serious[1,2,3]	no serious inconsistency	no serious indirectness	very serious[5]	none	6/39 (15.4%)	12.5%	RR 1.23 (0.41 to 3.7)	29 more per 1000 (from 74 fewer to 338 more)	⊕OOO VERY LOW	CRITICAL
UHU hospitalisation ≥6 months (follow-up 6 months; assessed with: Hospital admission self report)												
1	randomised trials	very serious[1,2,3]	no serious inconsistency	no serious indirectness	very serious[5]	none	4/39 (10.3%)	10%	RR 1.03 (0.28 to 3.82)	3 more per 1000 (from 72 fewer to 282 more)	⊕OOO VERY LOW	CRITICAL
School days lost ≥6 months (follow-up 6 months; assessed with: Self report (yes/no to any time off school))												
1	randomised trials	very serious[1,2,3]	no serious inconsistency	no serious indirectness	very serious[5]	none	20/38 (52.6%)	56.4%	RR 0.93 (0.62 to 1.4)	39 fewer per 1000 (from 214 fewer to 226 more)	⊕OOO VERY LOW	IMPORTANT
Parents' work days lost ≥6 months (follow-up 6 months; assessed with: Self report (yes/no to any work days lost))												
1	randomised trials	very serious[1,2,3]	no serious inconsistency	no serious indirectness	very serious[5]	none	13/39 (33.3%)	33.3%	RR 1 (0.53 to 1.87)	0 fewer per 1000 (from 157 fewer to 290 more)	⊕OOO VERY LOW	IMPORTANT

Controller medication use in patients who should have been on controller medications at baseline ≥6 months (follow-up 12 months; assessed with: i.e. persistent asthma)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	7/19 (36.8%)	16.7%	RR 2.21 (0.82 to 5.97)	202 more per 1000 (from 30 fewer to 830 more)	⊕⊕⊕O MODERATE	IMPORTANT
Persistent asthma on controllers at baseline but discontinued at 6 months (follow-up 12 months)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	6/42 (14.3%)	5.2%	RR 2.76 (0.73 to 10.42)	92 more per 1000 (from 14 fewer to 490 more)	⊕⊕OO LOW	IMPORTANT
Of those who met severity criteria for controllers at baseline, number on them at 12 months (follow-up 12 months)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	34/53 (64.2%)	61%	RR 1.05 (0.81 to 1.37)	30 more per 1000 (from 116 fewer to 226 more)	⊕⊕⊕O MODERATE	IMPORTANT

[1] *Method of randomisation and allocation concealment unclear*
[2] *Groups not comparable at baseline*
[3] *Underpowered*
[4] *Crosses one MID*
[5] *Crosses two MIDs*

Appendix J: Forest plots

J.1 Diagnosis: Signs and symptoms

J.1.1 Coupled sensitivity / specificity forest plots and ROC curves

J.1.1.1 Adults: symptoms vs. physician Dx and an objective test

Figure 47: Paroxsymal coughing

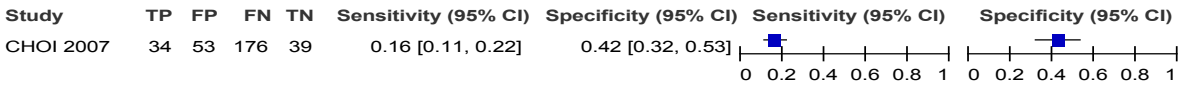


Figure 48: Dyspnoea without wheeze

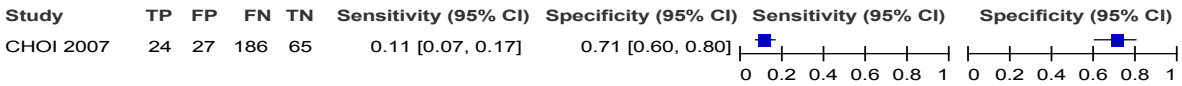


Figure 49: Wheeze without dyspnoea

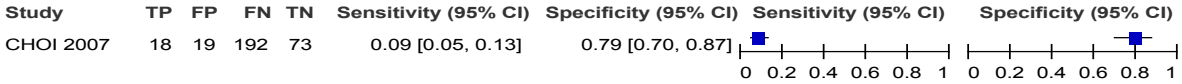


Figure 50: Diurnal cough

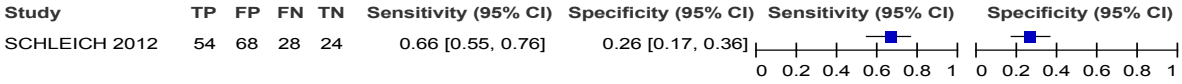


Figure 51: Nocturnal cough

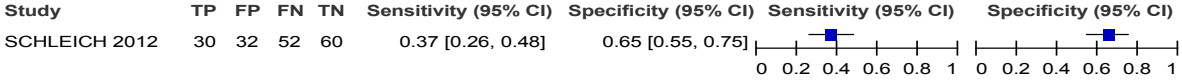


Figure 52: Diurnal wheeze

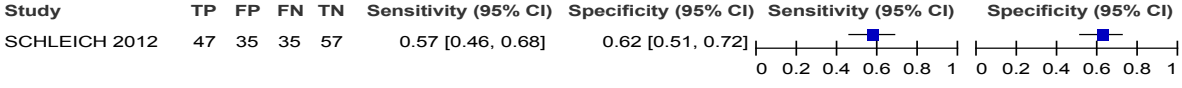


Figure 53: Nocturnal wheeze

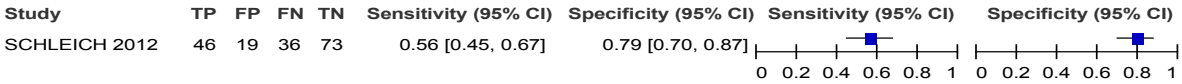


Figure 54: Dyspnoea

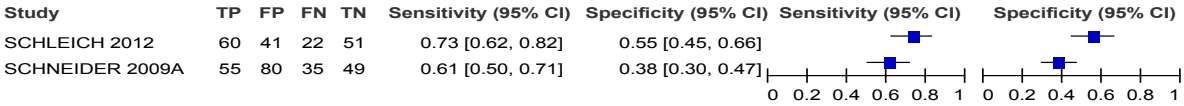


Figure 55: Wheeze

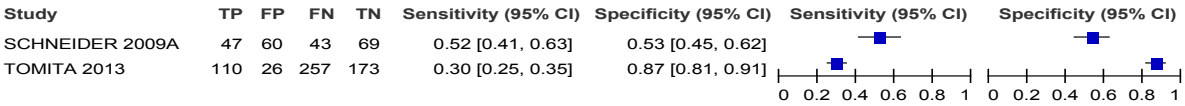


Figure 56: Cough

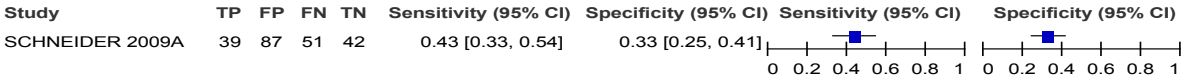


Figure 57: Nocturnal dyspnoea

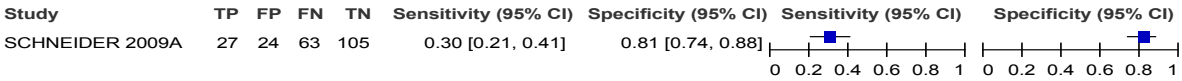


Figure 58: Diurnal symptoms

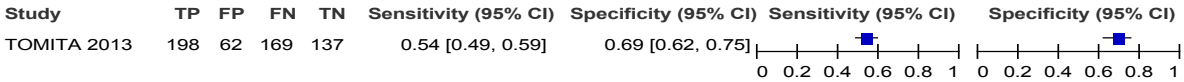


Figure 59: Total symptom score ≥5

CHOI 2007: numbers for 2x2 table not reported. Sensitivity 74.3%, Specificity 47.8%

Figure 60: Dyspnoea attacks

SCHNEIDER 2012: numbers for 2x2 table not reported. Sensitivity 40%, Specificity 78.4%

Figure 61: Dyspnoea going upstairs

SCHNEIDER 2012: numbers for 2x2 table not reported. Sensitivity 47.1%, Specificity 49.6%

Figure 62: Dyspnoea when walking

SCHNEIDER 2012: numbers for 2x2 table not reported. Sensitivity 4.8%, Specificity 93.2%

Figure 63: Dyspnoea on minimal exercise

SCHNEIDER 2012: numbers for 2x2 table not reported. Sensitivity 2.5%, Specificity 94.1%

Children <5 years: symptoms vs. physician Dx

Figure 64: Cough and wheeze

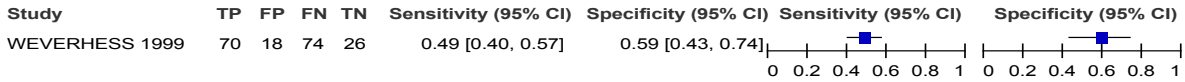


Figure 65: Dyspnoea

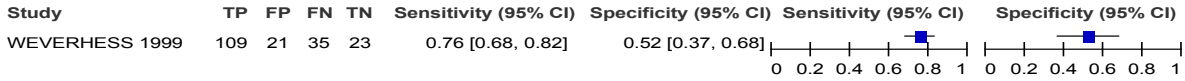


Figure 66: Wheeze

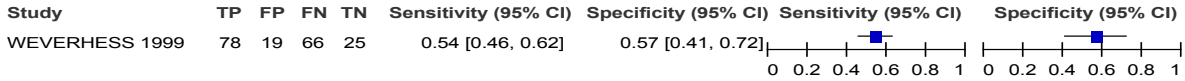
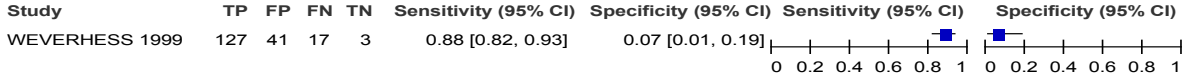


Figure 67: Cough



J.2 Diagnosis: History of atopic disorders

J.2.1 Coupled sensitivity / specificity forest plots and ROC curves

Figure 68: Adults: Personal history of atopic disorders

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
DEILAMI 2009	13	15	11	42	0.54 [0.33, 0.74]	0.74 [0.60, 0.84]
TOMITA 2013	202	64	165	135	0.55 [0.50, 0.60]	0.68 [0.61, 0.74]

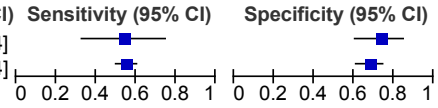


Figure 69: Adults: Family history of atopic disorders

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
CORDEIRO 2011	25	32	17	40	0.60 [0.43, 0.74]	0.56 [0.43, 0.67]
TOMITA 2013	95	34	272	165	0.26 [0.21, 0.31]	0.83 [0.77, 0.88]

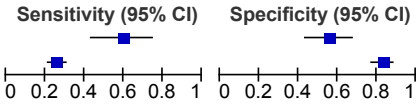


Figure 70: Children 5-16 years: Family history of asthma

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
VANDERMARK 2014	80	76	107	175	0.43 [0.36, 0.50]	0.70 [0.64, 0.75]

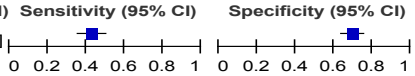


Figure 71: Children <5 years: Family history of atopic disorders

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
WEVER-HESS 1999	63	19	81	25	0.44 [0.36, 0.52]	0.57 [0.41, 0.72]

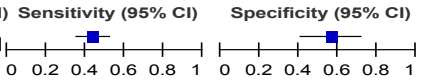


Figure 72: Children <5 years: Personal history of rhinitis

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
WEVER-HESS 1999	89	35	55	9	0.62 [0.53, 0.70]	0.20 [0.10, 0.35]

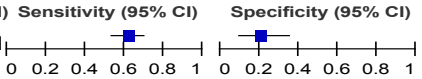
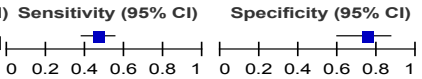


Figure 73: Children <5 years: Personal history of eczema

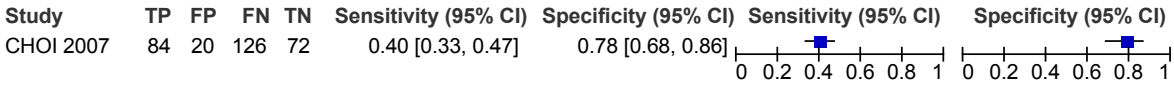
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
WEVER-HESS 1999	67	11	77	33	0.47 [0.38, 0.55]	0.75 [0.60, 0.87]



J.3 Diagnosis: Symptoms after exercise

J.3.1 Coupled sensitivity / specificity forest plots and ROC curves

Figure 74: Clinical history of symptoms in response to exercise vs Reference Standard (adults)



J.4 Diagnosis: Occupational asthma

J.4.1 Question whether symptoms are better away from work vs. reference standard

Figure 75: Asking whether their symptoms are better away from work (all causative agents)

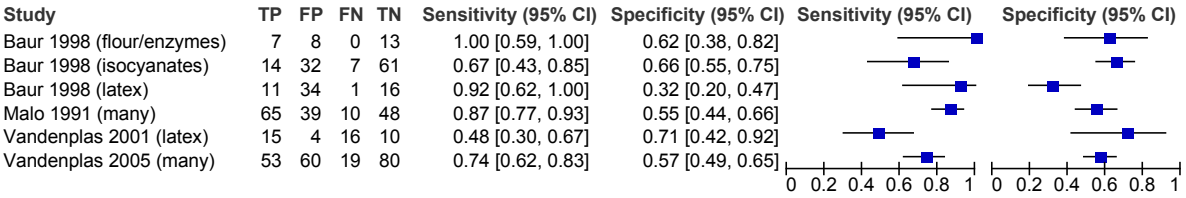


Figure 76: Improvement or disappearance of symptoms at weekend.

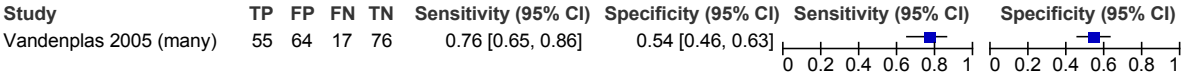


Figure 77: Improvement of disappearance of symptoms during vacation.

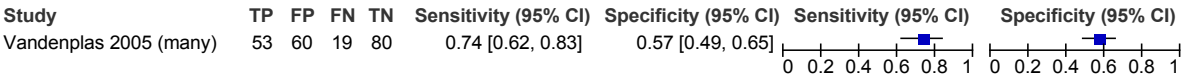


Figure 78: Symptoms better away from work (flour).

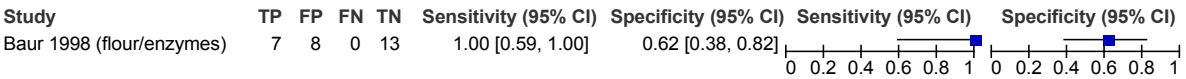


Figure 79: Symptoms better away from work (isocyanate).

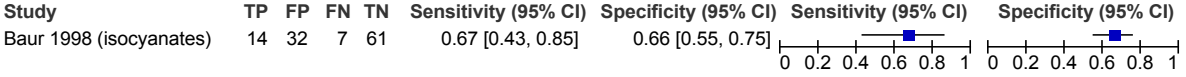


Figure 80: Symptoms better away from work (latex).

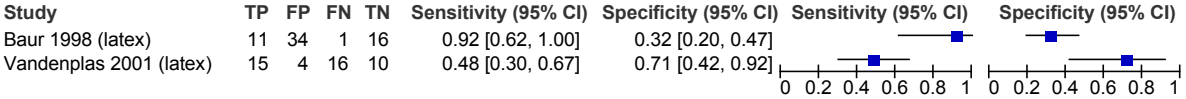
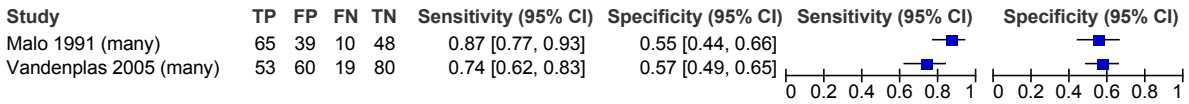


Figure 81: Symptoms better away from work (many causal agents).



J.5 Diagnosis: Spirometry

J.5.1.1 Coupled sensitivity / specificity forest plots and ROC curves

Adults: FEV1/FVC ratio measures

Figure 82: FEV1/FVC <70%

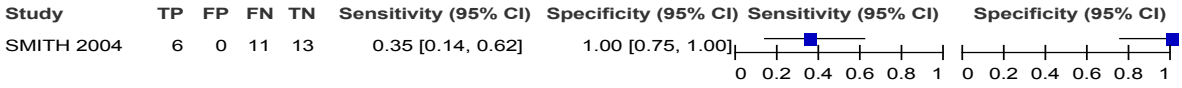
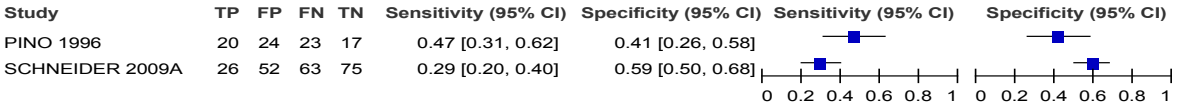
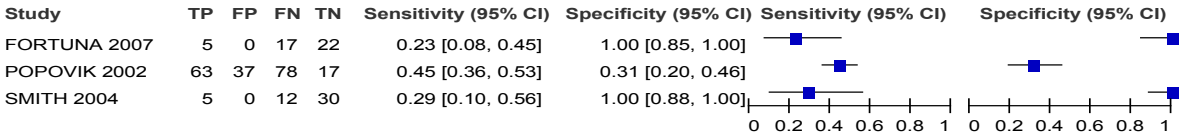


Figure 83: FEV1/FVC <70% and/or FEV1<80%



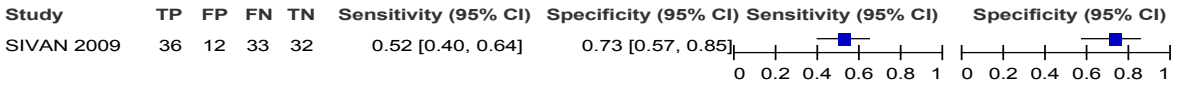
Adults: FEV1 only measures

Figure 84: FEV1 <80%



Children: FEV1 measures

Figure 85: FEV1 <80%



1 J.6 Diagnosis: Bronchodilator reversibility

2 J.6.1.1 Adults: Bronchodilator reversibility vs. Physician Dx

Figure 86: ΔFEV1%init ≥12% and ΔFEV1[L] ≥0.2L

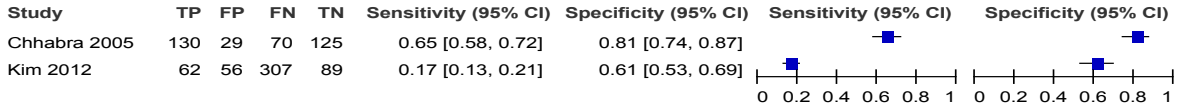
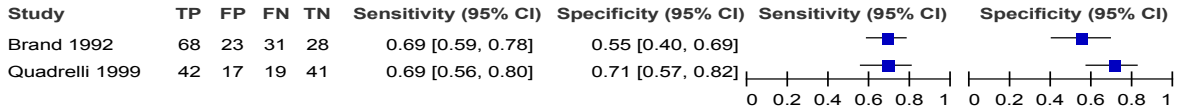


Figure 87: ΔFEV1%init >15% and ΔFEV1[L] >0.2L



J.7 Diagnosis: PEF variability

J.7.1.1 Adults > 16 years

Figure 88: Amp%mean (mean over 3 weeks >5%)

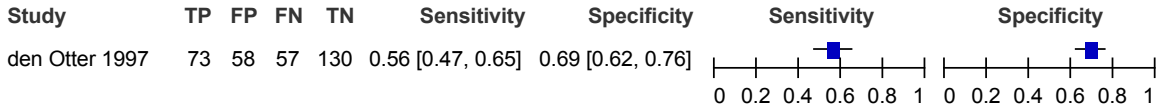


Figure 89: Amp%mean (mean over 3 weeks >10%)

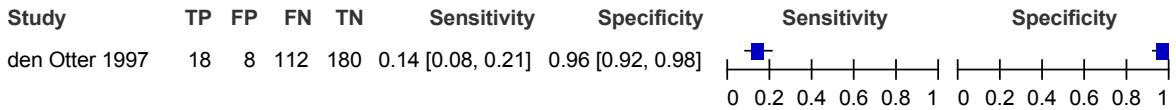


Figure 90: Amp%mean (mean over 3 weeks >15%)

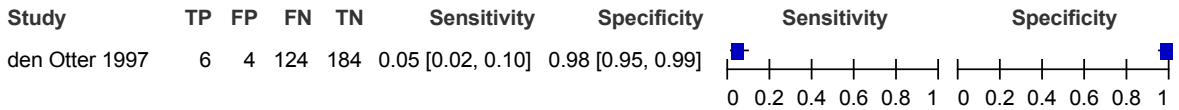


Figure 91: Amp%highest (>15% on 4 days or more)

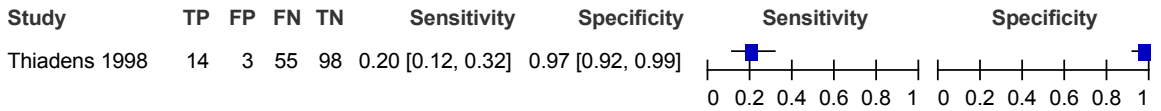


Figure 92: Amp%highest (>20% on 3 days or more)

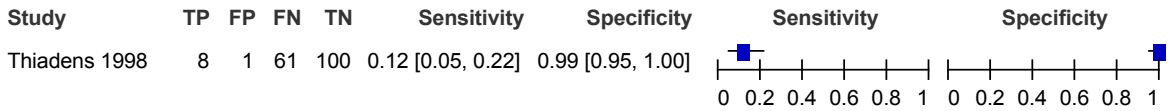


Figure 93: Amp%highest (mean over 2 weeks >10%)

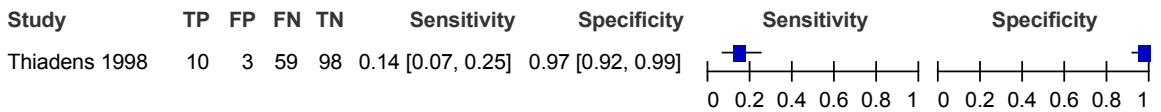
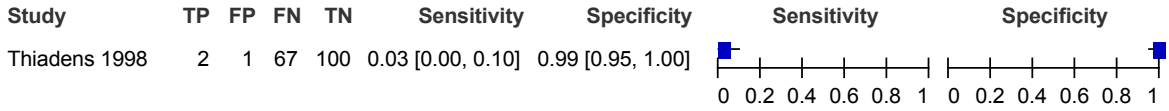


Figure 94: Amp%highest (mean over 2 weeks >10%)



J.7.1.2 Children 5-16 years

Figure 95: Amp%mean >12.3%

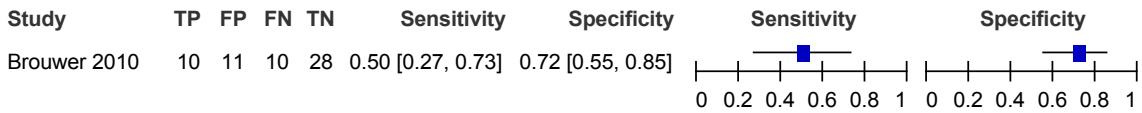


Figure 96: Amp%mean >20% versus PC20 histamine >16mg/mL.

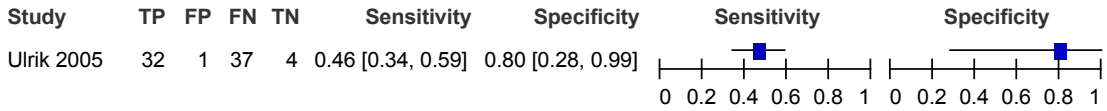
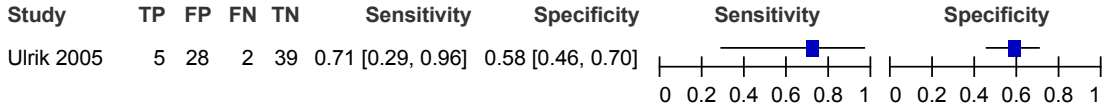


Figure 97: Amp%mean >20% versus bronchodilator reversibility change in FEV1 >10%.



J.8 Diagnosis: Skin prick tests

J.8.1.1 Skin prick tests vs. Physician Dx with objective test: ADULTS

Figure 98: D. pteronyssinus (Der P) +/- D. farinae (house dust mite)

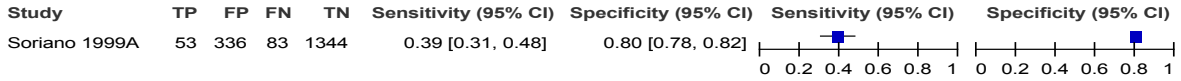


Figure 99: Alternaria temius (mould)

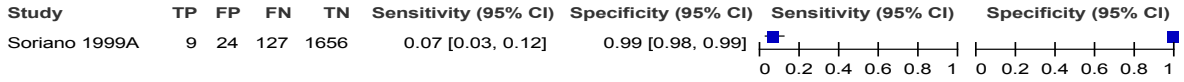


Figure 100: ≥1 positive from mixed allergens (mite and grass, plus ≥1 more of weed, tree, dust, cat, dog, feathers, mould, egg, milk)

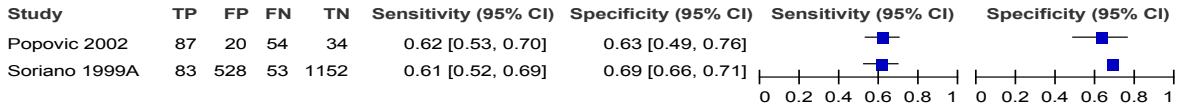


Figure 101: Grasses mixed or timothy only

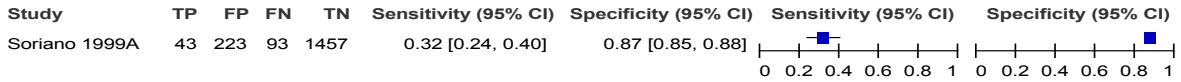


Figure 102: Cat

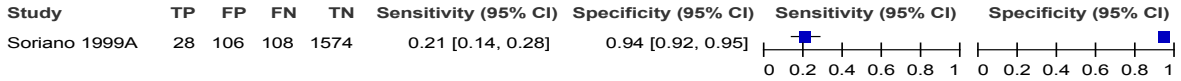
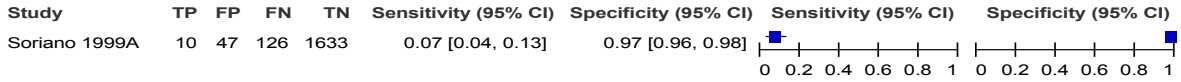


Figure 103: Cladosporium



J.8.1.2 Skin prick tests vs. Physician Dx with objective test: CHILDREN 5-16 years

Figure 104: D. pteronyssinus (Der P) +/- D. farinae (house dust mite)

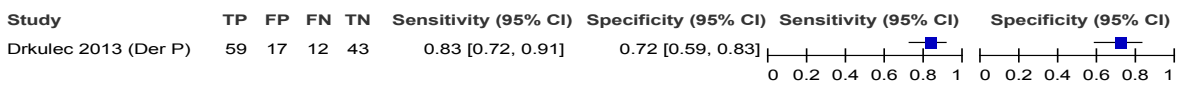
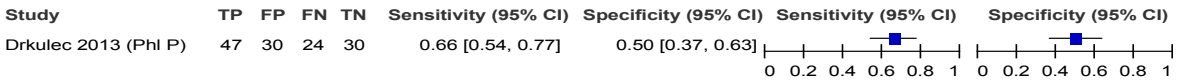
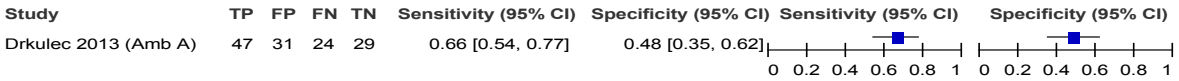


Figure 105: Phleum pratense (Phl P) timothy grass from Gramineae family



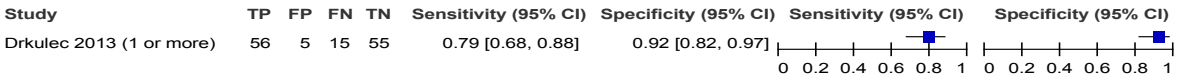
1

Figure 106: Ambrosia artemisifoliae (Amb A) common ragweed



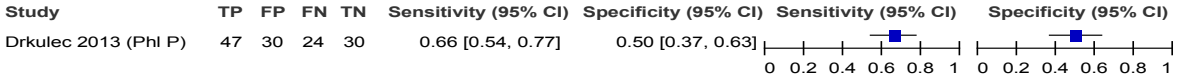
2

Figure 107: ≥1 positive from mixed allergens (mite and grass, plus ≥1 more of weed, tree, dust, cat, dog, feathers, mould, egg, milk)



3

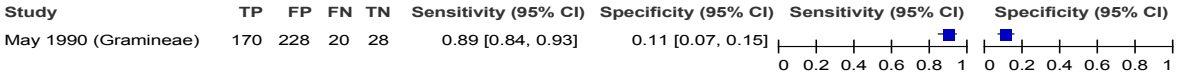
Figure 108: Grasses mixed or timothy only



4

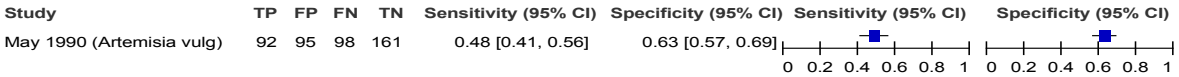
J.8.1.3 Skin prick tests vs. Physician Dx *without* objective test: ADULTS

Figure 109: Gramineae (grasses) both wild and cultivated



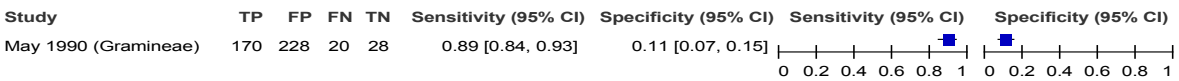
6

Figure 110: Artemisia vulgaris (mugwort)



7

Figure 111: Grasses mixed or timothy only .



8

J.8.1.4 Skin prick tests vs. Physician Dx *without* objective test: CHILDREN 5-16 years

Figure 112: D. pteronyssinus (Der P) +/- D. farinae (house dust mite)

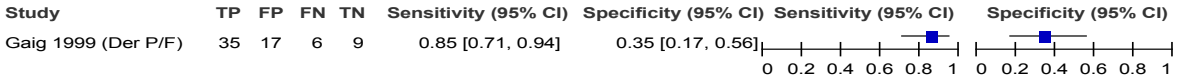
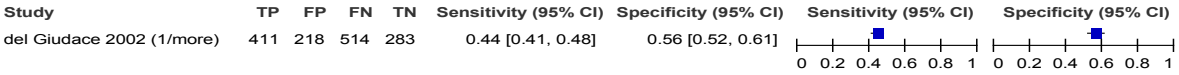


Figure 113: ≥1 positive from mixed allergens (mite and grass, plus ≥1 more of weed, tree, dust, cat, dog, feathers, mould, egg, milk).



J.9 Diagnosis: IgE

J.9.1.1 Adults: IgE vs. Physician Dx

Figure 114: DUST MITE specific IgE

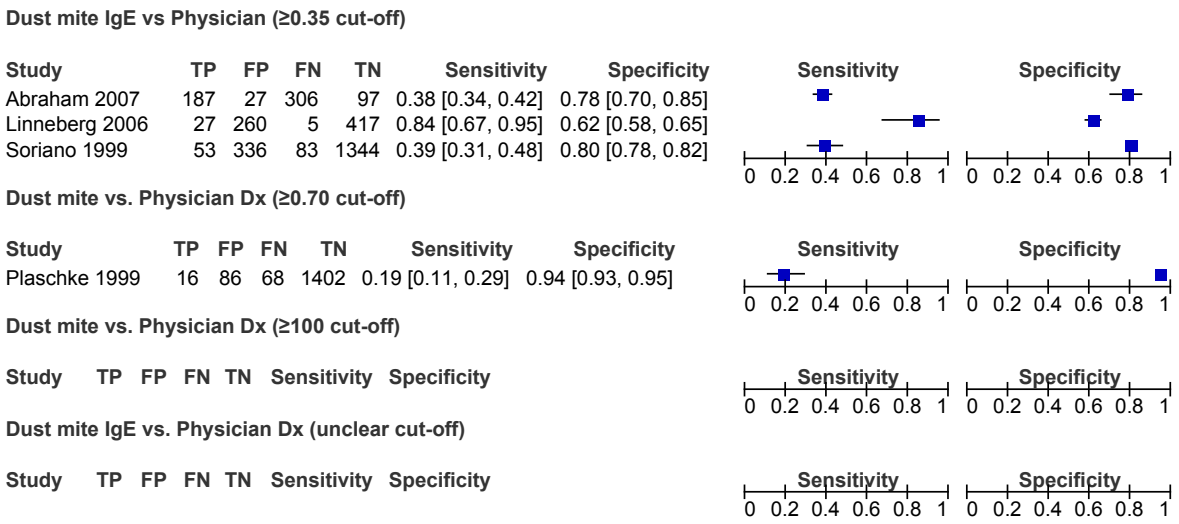


Figure 115: BIRCH specific IgE

Birch IgE vs. Physician Dx (≥0.35 cut-off)

Study	TP	FP	FN	TN	Sensitivity	Specificity

Birch IgE vs. Physician Dx (≥0.70 cut-off)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Plaschke 1999	25	155	59	1333	0.30 [0.20, 0.41]	0.90 [0.88, 0.91]

Birch IgE vs. Physician Dx (≥100 cut-off)

Study	TP	FP	FN	TN	Sensitivity	Specificity

Birch IgE vs. Physician Dx (unclear cut-off)

Study	TP	FP	FN	TN	Sensitivity	Specificity

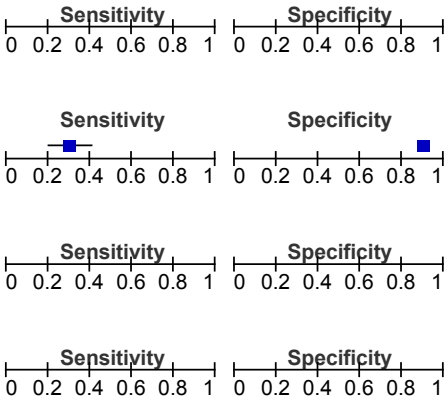


Figure 116: GRASSspecific IgE

Grass IgE vs. Physician Dx (≥0.35 cut-off)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Abraham 2007	164	24	329	100	0.33 [0.29, 0.38]	0.81 [0.73, 0.87]
Soriano 1999	93	223	43	1457	0.68 [0.60, 0.76]	0.87 [0.85, 0.88]

Grass IgE vs. Physician Dx (≥0.70 cut-off)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Plaschke 1999	30	187	54	1301	0.36 [0.26, 0.47]	0.87 [0.86, 0.89]

Grass IgE vs. Physician Dx (≥100 cut-off)

Study	TP	FP	FN	TN	Sensitivity	Specificity

Grass IgE vs. Physician Dx (unclear cut-off)

Study	TP	FP	FN	TN	Sensitivity	Specificity

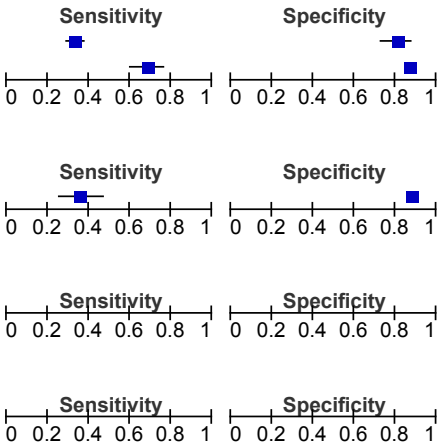


Figure 117: *ALTERNARIA*specific IgE

Alternaria IgE vs. Physician Dx (≥0.35 cut-off)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Abraham 2007	167	18	326	106	0.34 [0.30, 0.38]	0.85 [0.78, 0.91]

Alternaria IgE vs. Physician Dx (≥0.70 cut-off)

Study	TP	FP	FN	TN	Sensitivity	Specificity

Alternaria IgE vs. Physician Dx (≥100 cut-off)

Study	TP	FP	FN	TN	Sensitivity	Specificity

Alternaria IgE vs. Physician Dx (unclear cut-off)

Study	TP	FP	FN	TN	Sensitivity	Specificity

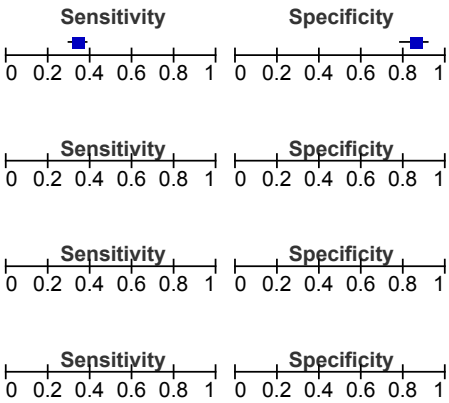


Figure 118: *CLADOSPORIUM* specific IgE

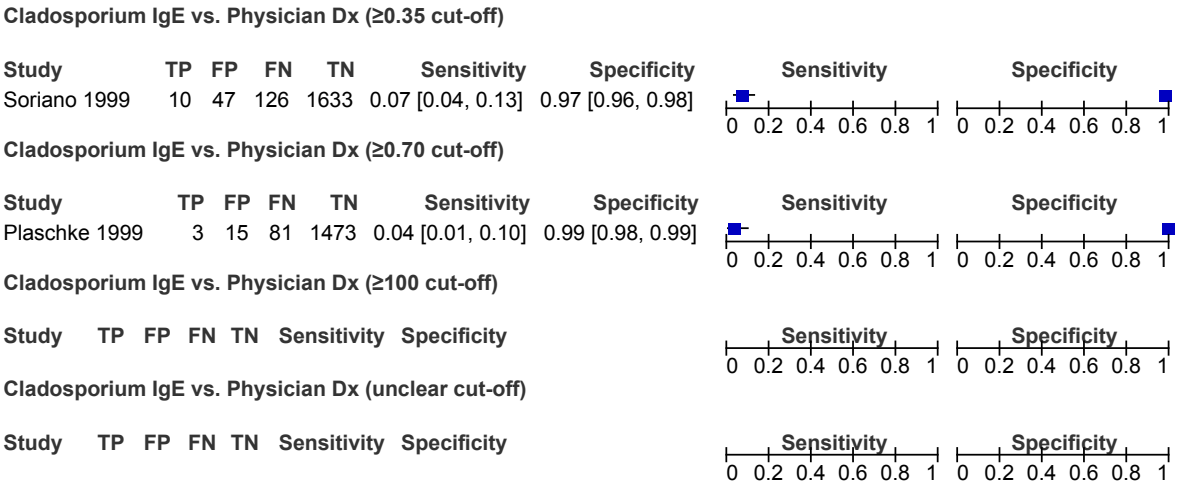
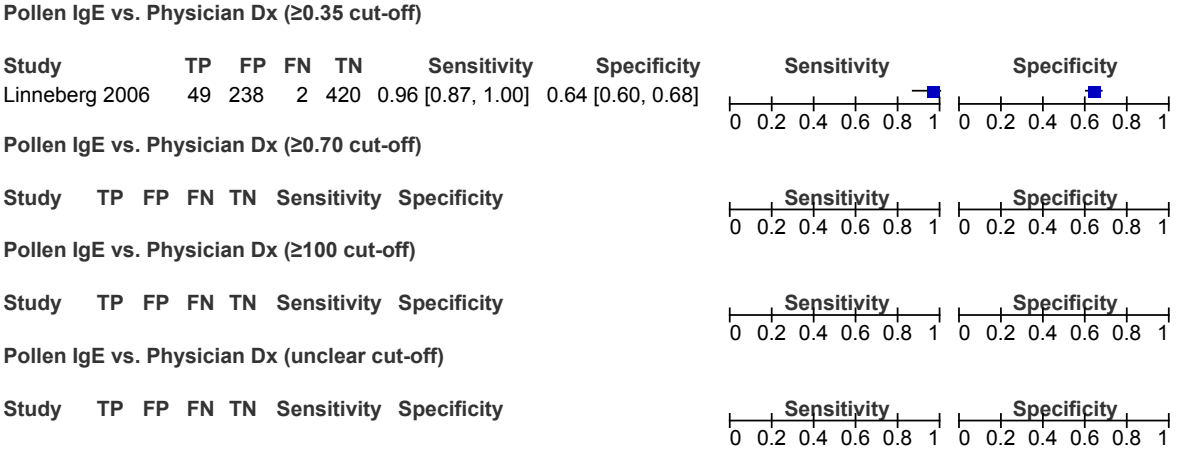


Figure 119: POLLEN specific IgE



1

Figure 120: TOTAL IgE

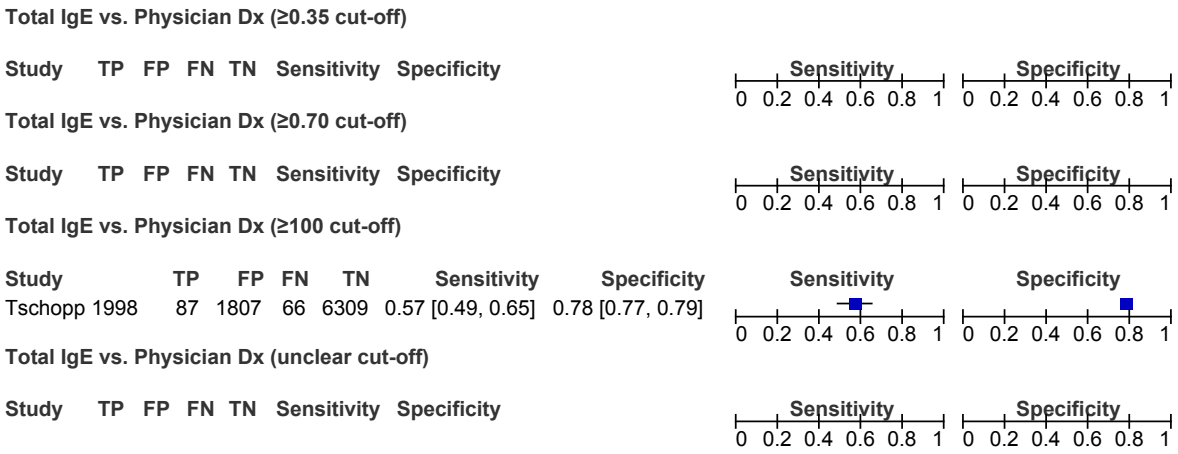


Figure 121: Cat IgE

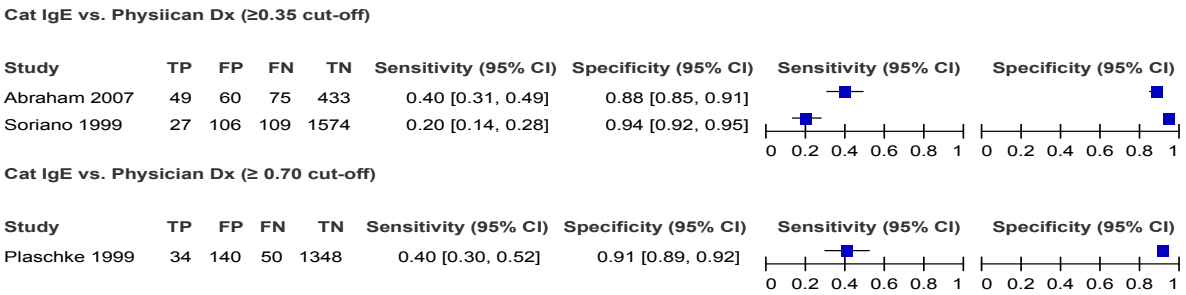
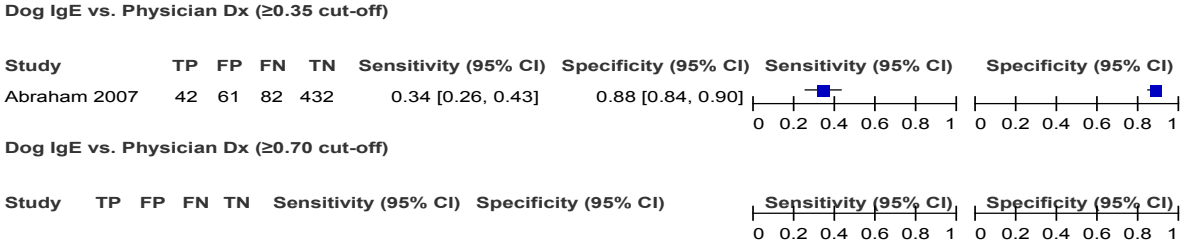


Figure 122: Dog IgE



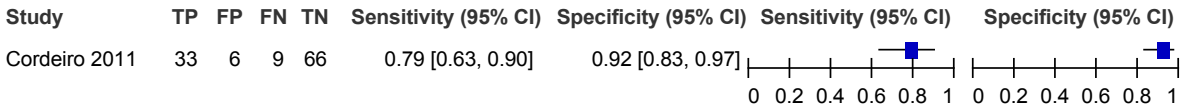
J.10 Diagnosis: FeNO

J.10.1.1 Coupled sensitivity / specificity forest plots and ROC curves

Forest plots: FeNO vs. Physician Dx with objective test

Adults

Figure 123: FeNO >27ppb



ADULTS: FeNO >30ppb

Voutilainen 2013. Number of TP, FP, FN and TN not provided.

Sensitivity: 43.0%; Specificity: 89.0%

Figure 124: FeNO >36ppb

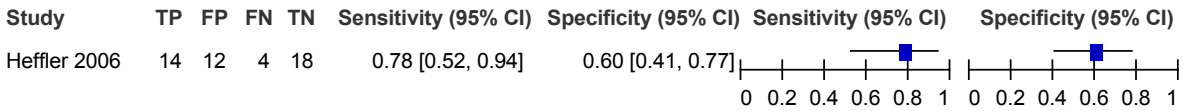


Figure 125: FeNO >38.8ppb

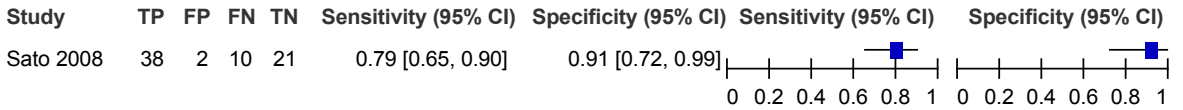
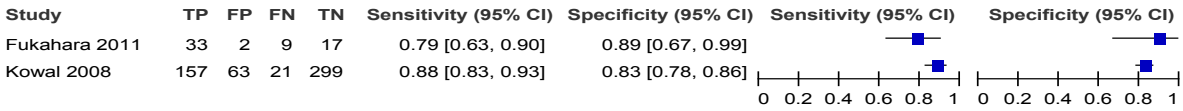


Figure 126: ADULTS: FeNO >40ppb



Children

Figure 127: CHILDREN: FeNO >22ppb

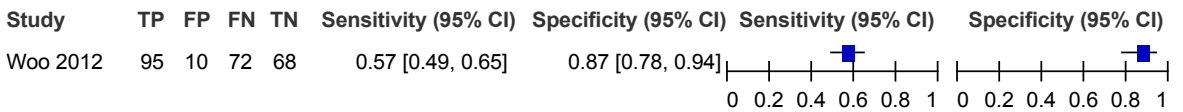
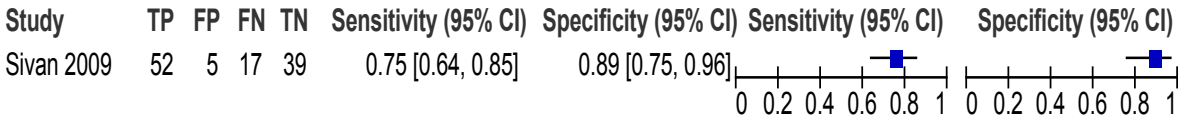
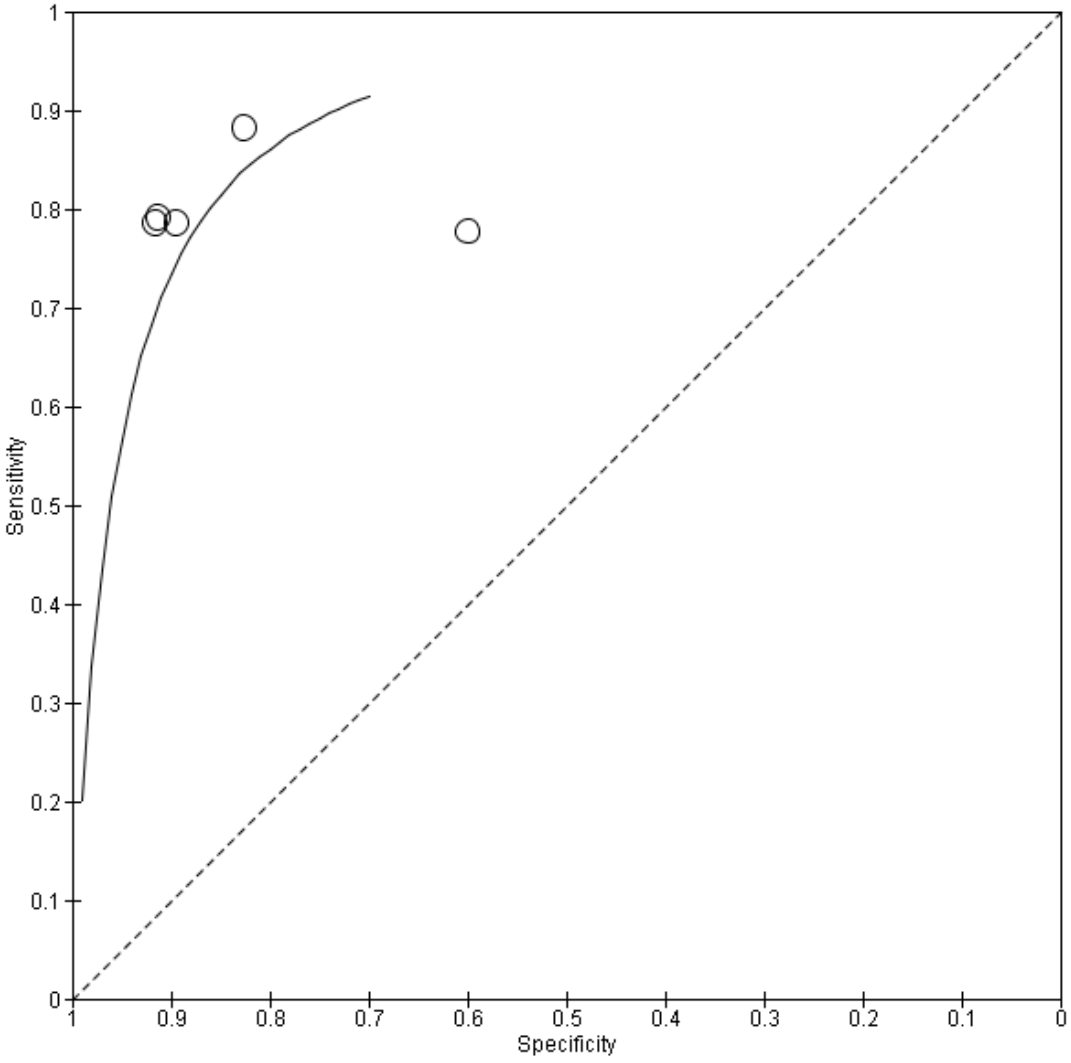


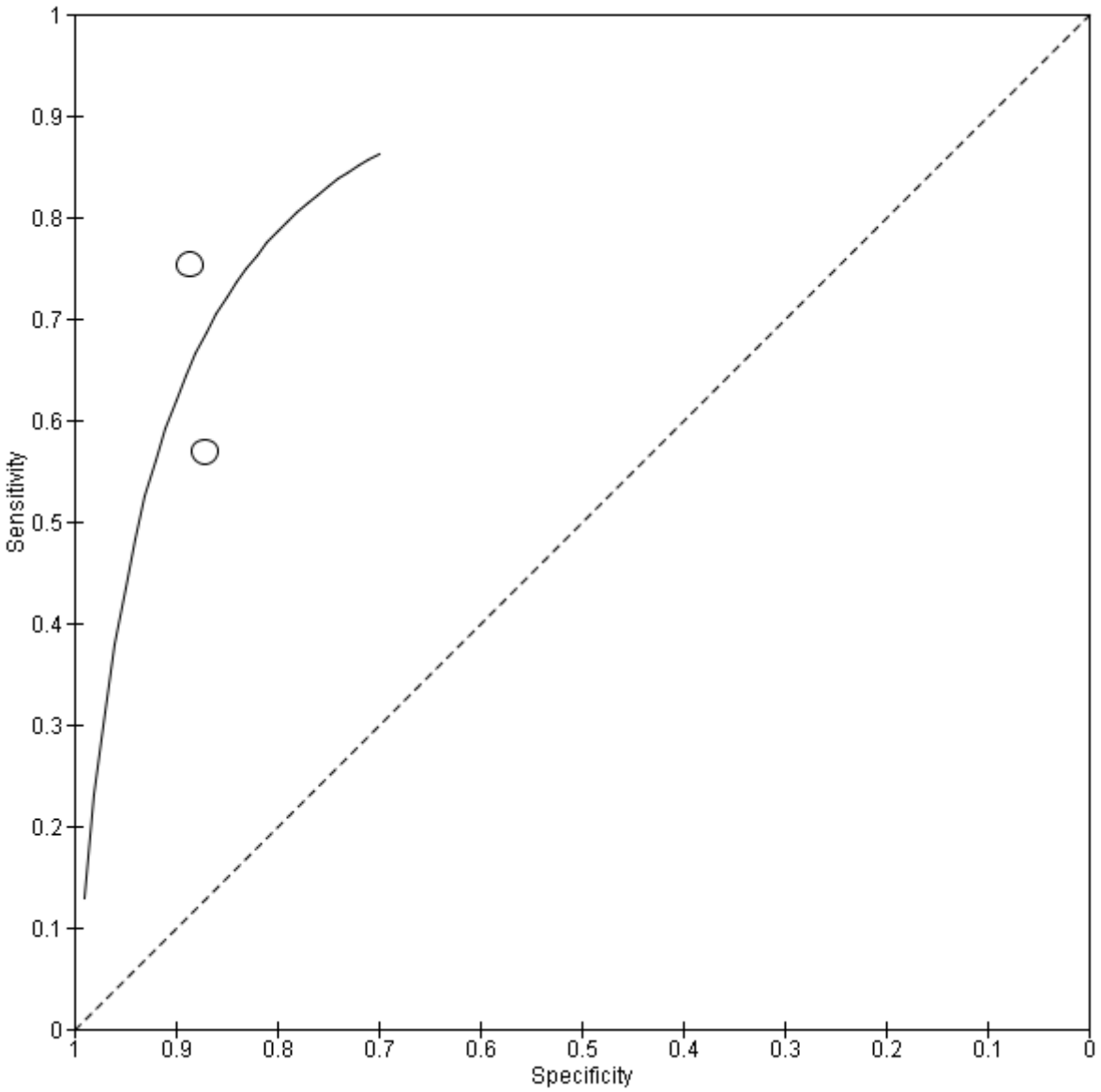
Figure 128: CHILDREN: FeNO 25ppb



Summary ROC Curve (fitted at a variety of test thresholds, selecting one threshold per study): Adults only



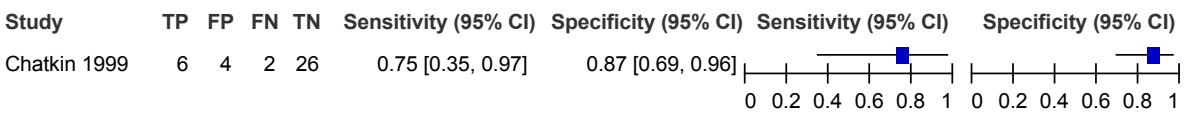
Summary ROC Curve (fitted at a variety of test thresholds, selecting one threshold per study): Children only



Forest plots: FeNO vs. other tests

ADULTS:

Figure 129: Adults: FeNO >30ppb versus methacholine ≤8mg/mL



FeNO levels

Table 205: FeNO levels – medians and means presented

Reference	Population and mean or median FeNO levels (ppb)								
	Asthma (bronchial, allergic or non-allergic)	Chronic cough	Bronchitis	Eosinophilic bronchitis	Rhinitis	GERD	Mixed non-asthma Dx	Healthy	Cough variant asthma
BERLYNE 2000	39	-	-	65.0	-	-	-	10	-
CARDINALE 2005	22.7 (children)	-	-	-	15.3 (children)	-	-	5.9 (children)	-
CHATKIN 1999**(also c-c study)	75.0	16.7	-	-	-	-	-	28.3	-
CIPRANDI 2013^	34 (children)	-	-	-	27 children	-	-	-	-
CORDEIRO 2011**$	44	-	-	-	21	-	17	-	-
DEYKIN 2002	57.9	-	-	-	-	-	-	26.3	-
FUKHARA 2011**	90.1	-	-	-	-	-	40.1	-	-
HEFFLER 2006**$ (also c-c study)	59.7	-	-	-	-	-	30.4	12.2	-
KOSTIKAS 2008**£(also c-c study)	24.0	-	-	-	17.5	-	11.0	11.0	-
KOWAL 2008**(also c-c study)	86	-	-	-	37	14.8	-	13	-
LOUHELAINEN 2008A	35.5 (children) 81.8 (adult)	- -	- -	-	- -	- -	- -	11.9 (children) 16.6 (adult)	-
SATO 2008**	93.5	-	16.4	-	-	-	21.2	-	-
SHIMODA 2013	92.6	-	-	-	-	-	-	18.0	35.6
SHOME 2006	24.8	-	-	-	-	-	-	5.9	-
WOO 2012**	23.4 (children)	-	-	-	-	-	12.6 (children)	-	-
VOUTILAINEN 2013**$	29.7	-	-	-	-	-	14.6	-	-
ZIETKOWSKI 2006A	64.9	-	-	-	-	-	-	12.9	-

Reference	Population and mean or median FeNO levels (ppb)								
	Asthma (bronchial, allergic or non-allergic)	Chronic cough	Bronchitis	Eosinophilic bronchitis	Rhinitis	GERD	Mixed non-asthma Dx	Healthy	Cough variant asthma
MEDIAN (range) ALL	50.95 (22.7-93.5)	16.7	16.4	65.0	21.0 (15.3-37.0)	14.8	17.0 (11.0-40.1)	12.6 (5.9-28.3)	35.6
MEDIAN (range) Adults/mixed	62.3 (24.0-93.5)	16.7	16.4	65.0	27 (17.5-37)	14.8	19.1 (11.0-40.1)	13.0 (5.9-28.3)	35.6
MEDIAN (range) Children only	28.7 (22.7-35.5)	-	-	-	21.2 (15.3-27)	-	12.6	8.9 (5.9-11.9)	-

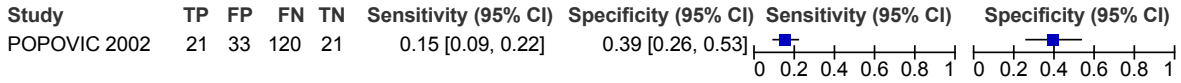
(a) *** is a sens/spec study*
(b) *^all patients have allergy (positive skin prick test)*
(c) *$ mixed population of adults and children*
(d) *£ excluding smokers*

J.11 Diagnosis: Eosinophils

J.11.1.1 ADULTS: PBE vs. Physician Dx

Figure 130: PBE ≥4.15%
TILEMANN 2011: 2x2 table not reported. Sensitivity 36%, specificity 83%

Figure 131: PBE cut-off not reported

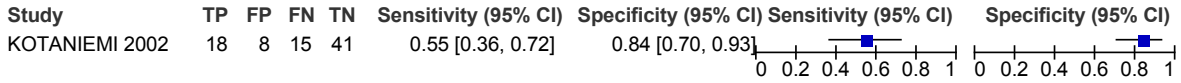


J.11.1.2 Children 5-16 years: PBE vs. Physician Dx

Figure 132: PBE >4%
SHIELDS 1999: 2x2 table not reported. Sensitivity 62%, specificity 67%

Figure 133: PBE >8%
SHIELDS 1999: 2x2 table not reported. Sensitivity 38%, specificity 93%

Figure 134: PBE ≥0.45 x 10^9/l



J.11.1.3 PBE counts

Table 206: Adults: PBE counts

Study	N	Counts	Units
PBE counts only			
BACKER 2002	624 (N=103 asthma)	Non-asthma: **0.19** Asthma: **0.26**	x10^9/L
HALVANI 2012	98 (N=61 asthma)	Healthy: **0.21** Asthma ICS: **0.40** Asthma no ICS: **0.52**	x10^9/L
HUNTER 2002	110 (N=89 asthma)	Healthy: **1.9** Pseudoasthma: **2.0** Asthma: **4.3**	%
KHAKZAD 2009	62 (N=50 asthma)	Healthy: **1.2** All asthma: **1.0** Mild intermittent: **2.0** Mild persistent: **3.6** Moderate persistent: **3.2** Severe: **3.2**	%
KROEGEL 1998	56 (N=14 asthma)	Healthy: **0.10** Bronchiectasis: **0.10**	x10^9/L median

Study	N	Counts	Units
		COPD: **0.12** Allergic asthma: **0.31**	
METSO 2000	190 (N=160 asthma)	Healthy: **0.13** Pre-Tx 1: **0.11** Pre-Tx 2: **0.14** Pre-Tx 3: **0.12**	$x10^9$/L
RYTILA 2000	68 (N=25 asthma)	Healthy: **0.11** Symptomatic: **0.17** All asthma: **0.41** Atopic asthma: **0.51** Non-atopic asthma: **0.27**	$x10^9$/L
TOMASIAKLOZOWSKA 2012	110 (N=91 asthma)	Healthy: **32.0** A stable – no ICS: **29.5** A stable - ICS: **42.4** A unstable – ICS: **49.8**	cells/mm^3
ZIETKOWSKI 2006A	140 (N=101 asthma)	Healthy: **119** A allergic: **247** A non-allergic: **211**	cells/mm^3
Median (range)	**Asthma** **Non-asthma****	**0.29 (0.10 - 0.52)** **3.2 (2.0 – 4.3)** **0.13 (0.10 – 0.21)** **1.9 (1.2 – 2.0)**	**$x10^9$/L** **%** **$x10^9$/L** **%**
Median (range)	**A – allergic** **A – non allergic**	**0.41 (0.31 – 0.51)** **0.27 (0.27)**	**$x10^9$/L** **$x10^9$/L**
Other results:	• 1 study showed that >50% of pts had PBE count >0.45 $x10^9$/L. • 2 studies showed that patients with asthma had higher PBE counts (cells/mm^3) than healthy controls (although stable asthma without ICS Tx was similar to healthy controls in 1 study). • 1 study showed that patients with allergic asthma had higher PBE counts (cells/mm^3) than patients with non-allergic asthma. • 1 study showed that patients with asthma treated with ICS had higher PBE counts (cells/mm^3) than patients with asthma not treated with ICS (regardless of whether the asthma was stable or unstable).		

*ICS = inhaled corticosteroid; A = allergic; Tx = treatment. *where applicable, all units have been converted into $x10^9$/L as these are the standard units used in current UK clinical practice. **this includes healthy controls*

Table 207: Children 5-16 years: PBE counts

Study	N	Counts	Units*	
PBE counts only				
LABBE 2001	143 (N=88 asthma)	Healthy: **0.25** Chronic cough: **0.21** Asthma: **0.40**	$x10^9$/L	Children (mean 7 yrs)

Study	N	Counts	Units*	
NORDLUND 2012	39	Asthma (mild/mod): **0.25**	x10^9/L	Children (mean 14 yrs)
SILVESTRI 2001A	112	Allergic: **500, 7.5%** Non-allergic: **125, 2.5%**	Cells/mm^3 and %	Children (mean 11 yrs)
SILVESTRI 2003	92	All: **5.5%** Atopic: **6.7%** Non-atopic: **3.0%**	%	Children (mean 11 yrs)
TUCHINDA 1987	1000	0 – 500 = **40%** 501-1000 = **29%** 1001-1500 = **16%** 1501-2000 = **9%** >2000 = **7%**	Cells/mm^3	Children <13 years (mean not reported)
VILA-INDURAIN 1999	57 (N=36 asthma)	• Healthy: **161** • Asthma (norm FEV_1): **509** • Asthma (< norm FEV_1 , norm with SABA): **397** • Asthma (< norm FEV_1 , not norm with SABA): **319**	Cells/mm^3	Children (8-18 yrs, mean not reported)
Mean (range)	**Asthma** **Non-asthma****	**0.33 (0.25 – 0.40)** **5.5 (5.5)** **0.23 (0.21 – 0.25)** -	**x10^9/L** **%** **x10^9/L** **%**	
	A – allergic **A - nonallergic**	- **7.1 (6.7 – 7.5)** - **2.8 (2.5 – 3.0)**	**x10^9/L** **%** **x10^9/L** **%**	
Other results:	• 1 study showed that the % of pts decreased with increasing PBE cell counts (0-500 cells/mm^3 had the most pts, with >2000 cells/mm^3 having the least). • 1 study showed that patients with asthma had higher PBE counts (cells/mm^3) than healthy controls • 1 study showed that patients with allergic asthma had higher PBE counts (cells/mm^3) than patients with non-allergic asthma • 1 study showed that patients with asthma with a normal FEV_1 had higher PBE counts (cells/mm^3) than patients with asthma with <normal FEV_1 (regardless of whether the FEV_1 normalised with SABA).			

*SABA = short-acting beta-agonists; *where applicable, all units have been converted into x10^9/L as these are the standard units used in current UK clinical practice. **this includes healthy controls*

Table 208: Children <5 years: PBE counts

Study	N	Counts	Units	
PBE counts only				
PIIPPOSAVOLAINEN 2007	83	Asthma: 0.1	10^9/L	Children (<2 yrs, mean not reported)

Study	N	Counts		Units	
Median		Asthma	0.1	10^9/L	
Range of means		Asthma	0.1	10^9/L	

1 J.12 Diagnosis: Histamine and methacholine challenge tests

2 J.12.1.1 Coupled sensitivity / specificity forest plots and ROC curves

3 Adults: Methacholine/Histamine Challenge Tests vs Reference Standard

Figure 135: PC20 ≤8mg/ml

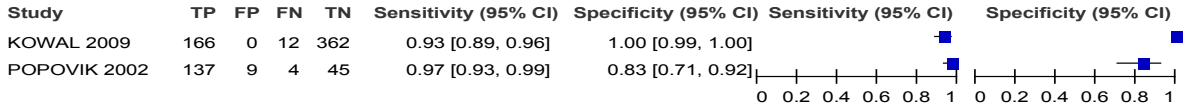


Figure 136: PD20 ≤6900µg

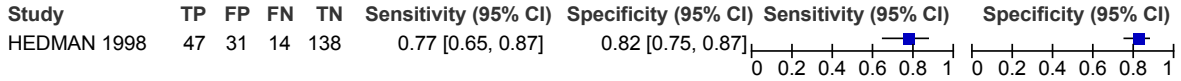
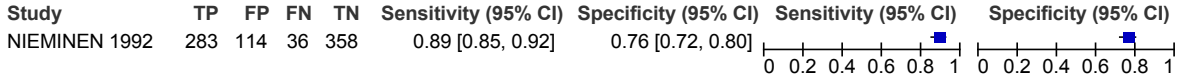


Figure 137: PD20 ≤2600µg



4

Children: Methacholine/Histamine Challenge Tests vs Reference Standard

Figure 138: Age <18 yrs- PC20 ≤16mg/ml

Data unsuitable for RevMan:

ANDERSON 2009 (n=115; MCT cut-off 16mg/ml): Sensitivity 66.2%; Specificity = 62.9%

Methacholine/Histamine Challenge Tests vs Other Tests

Figure 139: Histamine Challenge Test vs Mannitol (adults)- PD15≤1mg

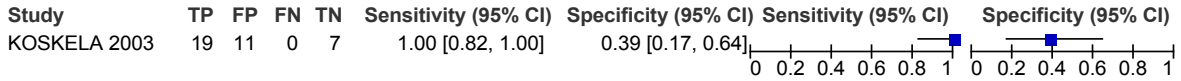


Figure 140: Histamine Challenge Test vs Mannitol (adults) - PD15≤0.4mg

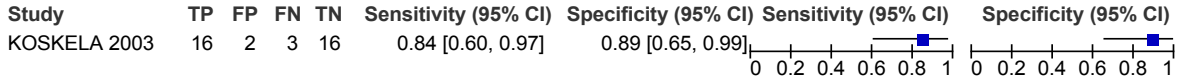


Figure 141: Histamine Challenge Test vs Mannitol (<18 yrs)

No data found on sensitivity or specificity

J.13 Diagnosis: Mannitol challenge test

J.13.1.1 Coupled sensitivity / specificity forest plots

Mannitol Challenge Test vs Reference Standard

Figure 142: Mannitol Challenge Test vs Reference Standard (all age groups)≥15% fall in FEV1 ≤635mg or 10% fall between consecutive doses

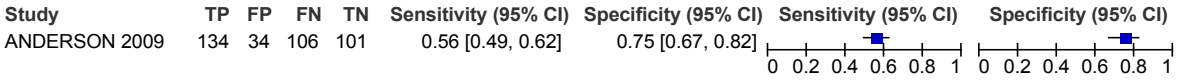


Figure 143: Mannitol Challenge Test vs Reference Standard (<18 yrs) ≥15% fall in FEV1 ≤635mg or 10% fall between consecutive doses

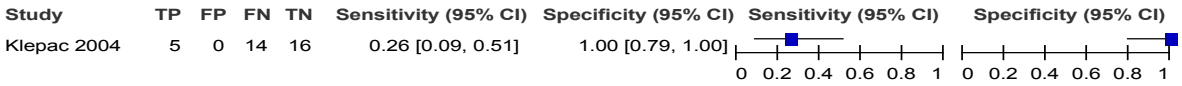
Data unsuitable for RevMan:

1. ANDERSON 2009: Sensitivity 63.2%; Specificity = 81.4%

J.14 Diagnosis: Exercise challenge test

J.14.1.1 Exercise test vs. Physician Dx: ADULTS

Figure 144: Exercise test ΔFEV1≥10%



J.14.1.2 Exercise test vs. other tests: ADULTS

Figure 145: Exercise test ΔFEV1 ≥18% vs. methacholine

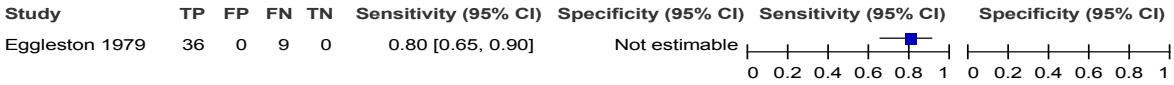
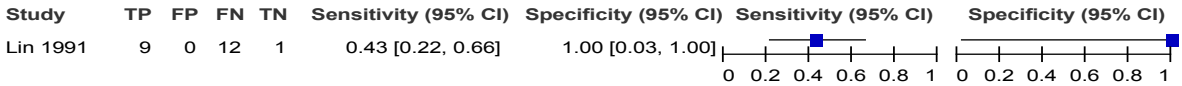


Figure 146: Exercise test ΔFEV1 ≥20% vs. methacholine



J.14.1.3 Exercise test vs. other tests: CHILDREN 5-16 years

Figure 147: Cold air exercise test ΔFEV1 % init >15% vs. mannitol ΔFEV1 % init >15%.

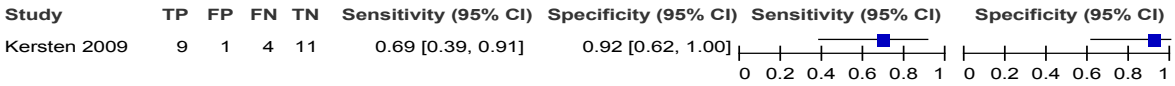
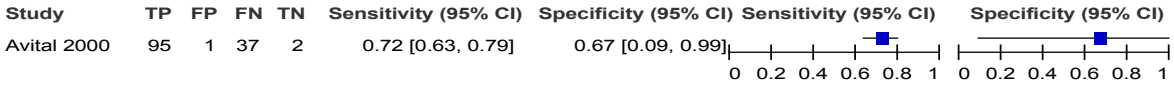


Figure 148: Exercise ΔFEV1 ≥8.2% vs. methacholine PC20 ≤8mg/mL



J.15 Monitoring: Questionnaires

J.15.1.1 Children (5-16 years) with uncontrolled asthma: Monitoring questionnaires + treatment vs UC + treatment.

Figure 149: QOL <6 months (PAQLQ; scale 1-7)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
RIKKERS 2012	0.4	0.1173	100.0%	0.40 [0.17, 0.63]
Total (95% CI)			**100.0%**	**0.40 [0.17, 0.63]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.41 (P = 0.0006)

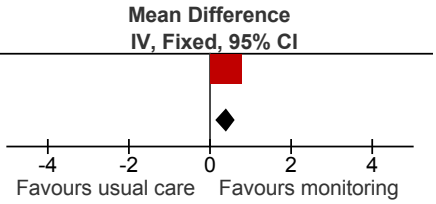


Figure 150: QOL ≥6 months (PAQLQ; range 1-7)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
RIKKERS 2012	-0.05	0.2296	100.0%	-0.05 [-0.50, 0.40]
Total (95% CI)			**100.0%**	**-0.05 [-0.50, 0.40]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.22 (P = 0.83)

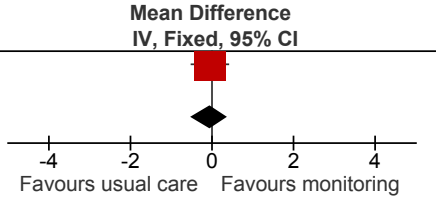


Figure 151: Exacerbations (OCS) ≥6 months

Study or Subgroup	Monitoring control Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RIKKERS 2012	6	35	6	40	100.0%	1.14 [0.41, 3.22]
Total (95% CI)		**35**		**40**	**100.0%**	**1.14 [0.41, 3.22]**
Total events	6		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.25 (P = 0.80)

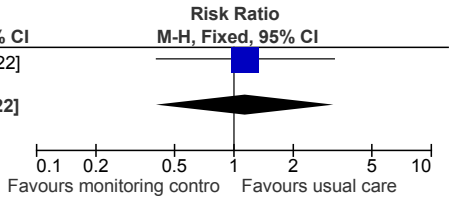


Figure 152: Asthma control <6 months (ACQ, range 0-6)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
RIKKERS 2012	-0.32	0.1225	100.0%	-0.32 [-0.56, -0.08]
Total (95% CI)			**100.0%**	**-0.32 [-0.56, -0.08]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.61 (P = 0.009)

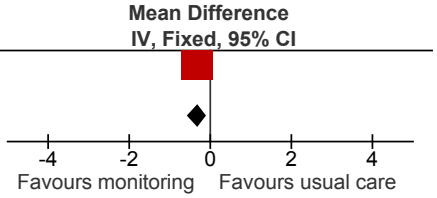


Figure 153: Asthma control ≥6 months (ACQ, range 0-6)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
RIKKERS 2012	-0.05	0.1531	100.0%	-0.05 [-0.35, 0.25]
Total (95% CI)			**100.0%**	**-0.05 [-0.35, 0.25]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)

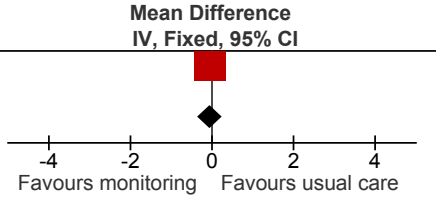


Figure 154: Lung Function <6 months (FEV1 L)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
RIKKERS 2012	0.23	0.0765	100.0%	0.23 [0.08, 0.38]
Total (95% CI)			**100.0%**	**0.23 [0.08, 0.38]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.01 (P = 0.003)

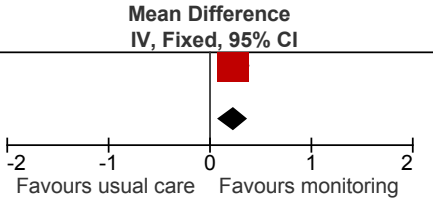


Figure 155: Lung Function ≥6 months (FEV1 L)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
RIKKERS 2012	0.1	0.1071	100.0%	0.10 [-0.11, 0.31]
Total (95% CI)			**100.0%**	**0.10 [-0.11, 0.31]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.93 (P = 0.35)

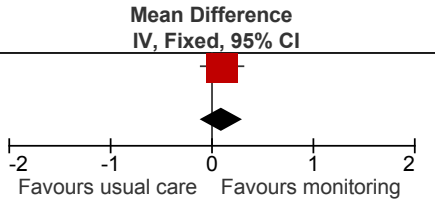


Figure 156: Symptom free days <6 months (% over 2 weeks)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
RIKKERS 2012	-1.5	6.6328	100.0%	-1.50 [-14.50, 11.50]
Total (95% CI)			**100.0%**	**-1.50 [-14.50, 11.50]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.82)

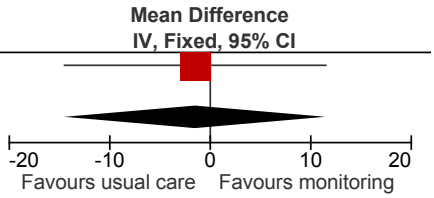


Figure 157: Symptom free days ≥6 months (% over 2 weeks)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
RIKKERS 2012	4	6.9899	100.0%	4.00 [-9.70, 17.70]
Total (95% CI)			**100.0%**	**4.00 [-9.70, 17.70]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.57 (P = 0.57)

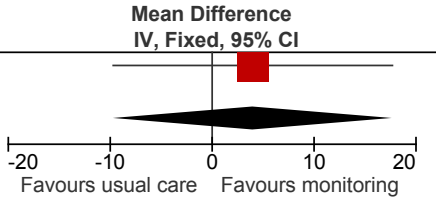


Figure 158: ICS use <6 months (mean daily dose)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
RIKKERS 2012	14	47.4499	100.0%	14.00 [-79.00, 107.00]
Total (95% CI)			**100.0%**	**14.00 [-79.00, 107.00]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.30 (P = 0.77)

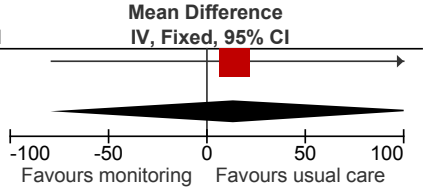
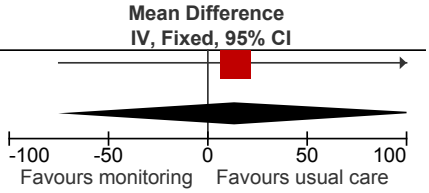


Figure 159: ICS use ≥6 months (mean daily dose)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
RIKKERS 2012	14	45.409	100.0%	14.00 [-75.00, 103.00]
Total (95% CI)			**100.0%**	**14.00 [-75.00, 103.00]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.31 (P = 0.76)



J.15.1.2 Adults and young people (>16 years) overall: Monitoring questionnaires + treatment vs UC + treatment.

Figure 160: QOL ≥6 months (PAQLQ; range 1-7)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
MEER 2009	0.38	0.0918	67.7%	0.38 [0.20, 0.56]
MEHUYS 2008	0.2	0.133	32.3%	0.20 [-0.06, 0.46]
Total (95% CI)			**100.0%**	**0.32 [0.17, 0.47]**

Heterogeneity: Chi² = 1.24, df = 1 (P = 0.27); I² = 19%
Test for overall effect: Z = 4.26 (P < 0.0001)

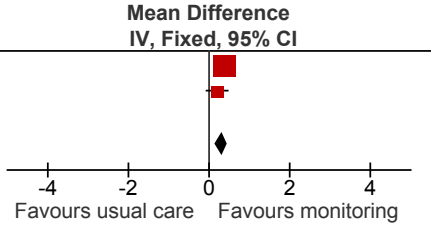


Figure 161: Exacerbations (OCS) ≥6 months

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
MEER 2009	0.1655	0.428	100.0%	1.18 [0.51, 2.73]
Total (95% CI)			**100.0%**	**1.18 [0.51, 2.73]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.70)

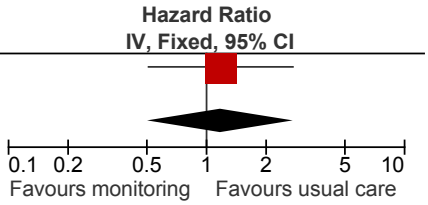


Figure 162: Exacerbations (OCS, ER or hospitalisation) ≥6 months

Study or Subgroup	Monitoring control Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
MEER 2009	11	91	10	92	53.8%	1.11 [0.50, 2.49]
MEHUYS 2008	10	80	8	70	46.2%	1.09 [0.46, 2.62]
Total (95% CI)		**171**		**162**	**100.0%**	**1.10 [0.61, 1.99]**
Total events	21		18			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%
Test for overall effect: Z = 0.33 (P = 0.74)

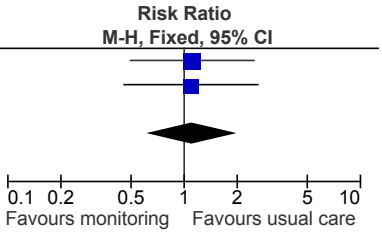


Figure 163: UHU (ER or hospitalisation) ≥6 months

Study or Subgroup	Monitoring control Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
MEHUYS 2008	1	80	5	70	100.0%	0.17 [0.02, 1.46]
Total (95% CI)		**80**		**70**	**100.0%**	**0.17 [0.02, 1.46]**
Total events	1		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.61 (P = 0.11)

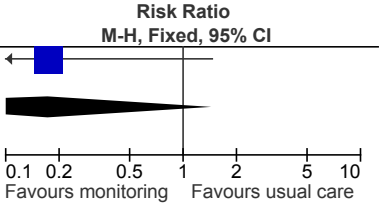


Figure 164: Asthma control <6 months (ACT, range 5-25)

Study or Subgroup	Monitoring control Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
MEHUYS 2008	20.3	3.2	99	20	3.8	84	100.0%	0.30 [-0.73, 1.33]
Total (95% CI)			**99**			**84**	**100.0%**	**0.30 [-0.73, 1.33]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.57 (P = 0.57)

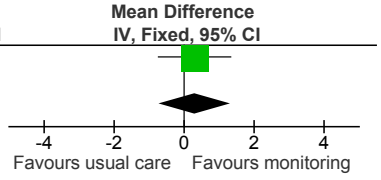


Figure 165: Asthma control ≥6 months (ACT, range 5-25)

Study or Subgroup	Monitoring control Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
MEHUYS 2008	20.2	3.5	80	19.7	4.8	70	100.0%	0.50 [-0.86, 1.86]
Total (95% CI)			**80**			**70**	**100.0%**	**0.50 [-0.86, 1.86]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)

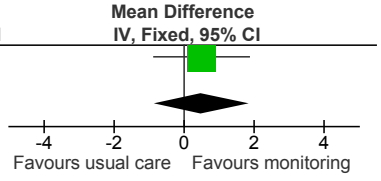


Figure 166: Asthma control ≥6 months (ACQ, range 0-6)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
MEER 2009	-0.47	0.0867	100.0%	-0.47 [-0.64, -0.30]
Total (95% CI)			**100.0%**	**-0.47 [-0.64, -0.30]**

Heterogeneity: Not applicable
Test for overall effect: Z = 5.42 (P < 0.00001)

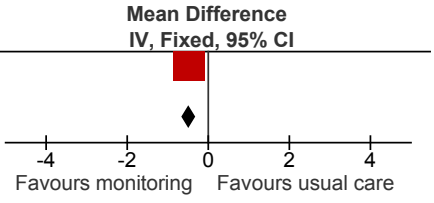


Figure 167: Lung Function ≥6 months (FEV1 L)

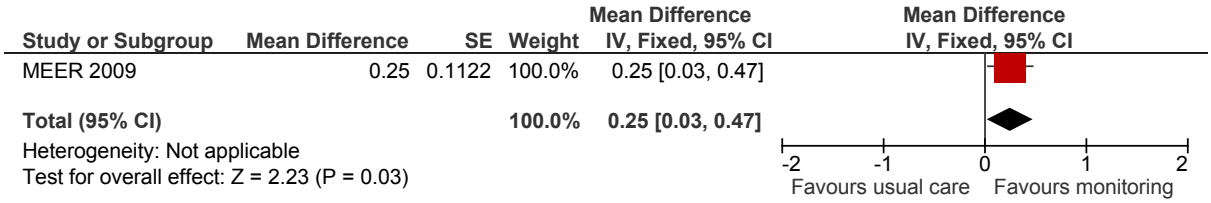
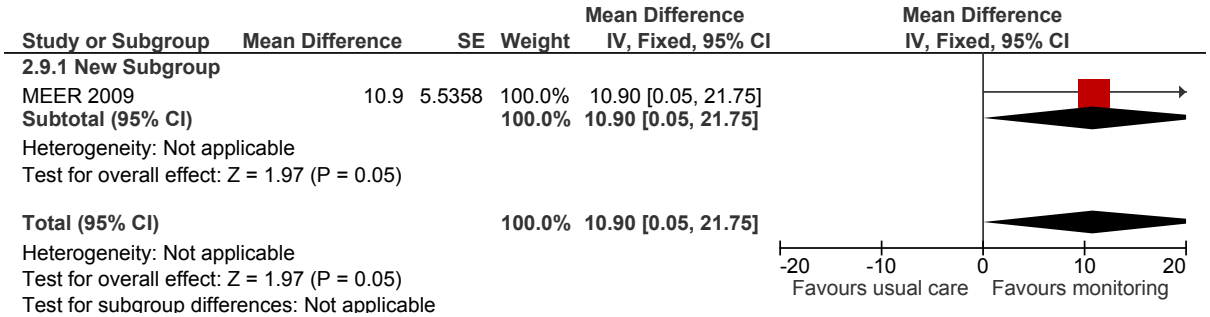


Figure 168: Symptom free days ≥6 months (% over 2 weeks)



1

Figure 169: ICS use ≥6 months (mean daily dose)

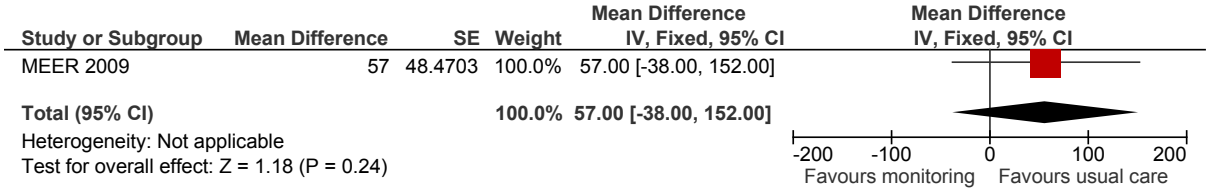


Figure 170: Rescue medication <6 months (mean puffs/day)

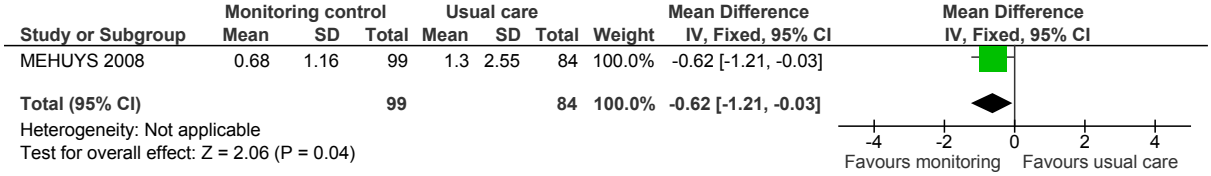
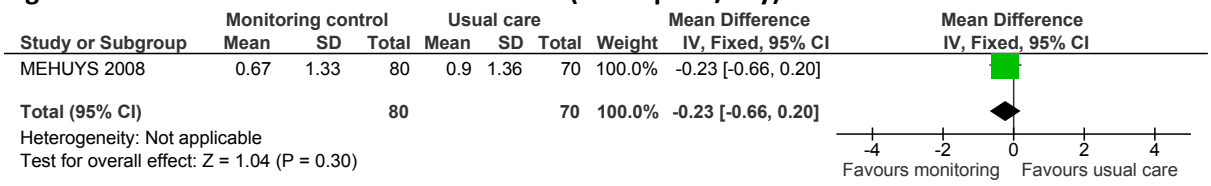


Figure 171: Rescue medication ≥6 months (mean puffs/day)



2
3

1 J.16 Monitoring: Lung function test

2 J.16.1.1 Adults: Monitoring PEF versus symptom monitoring

Figure 172: QOL ≥6 months (AQLQ increase more than 0.5 points)

Study or Subgroup	PEF monitoring Events	Total	Symptom monitoring Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Buist 2006	52	134	50	128	100.0%	0.99 [0.73, 1.35]
Total (95% CI)		**134**		**128**	**100.0%**	**0.99 [0.73, 1.35]**
Total events	52		50			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.04 (P = 0.97)

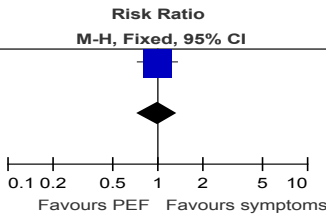


Figure 173: QOL ≥6 months (AQLQ decrease more than 0.5 points)

Study or Subgroup	PEF monitoring Events	Total	Symptom monitoring Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Buist 2006	16	134	11	128	100.0%	1.39 [0.67, 2.88]
Total (95% CI)		**134**		**128**	**100.0%**	**1.39 [0.67, 2.88]**
Total events	16		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.88 (P = 0.38)

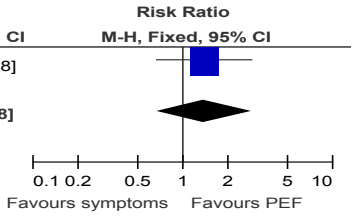


Figure 174: Exacerbations ≥6 months (OCS)

Study or Subgroup	PEF monitoring Events	Total	Symptom monitoring Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Charlton 1990	14	27	7	33	56.7%	2.44 [1.15, 5.18]
Turner 1998	3	44	6	48	43.3%	0.55 [0.15, 2.05]
Total (95% CI)		**71**		**81**	**100.0%**	**1.28 [0.29, 5.57]**
Total events	17		13			

Heterogeneity: Tau² = 0.85; Chi² = 3.81, df = 1 (P = 0.05); I² = 74%
Test for overall effect: Z = 0.33 (P = 0.74)

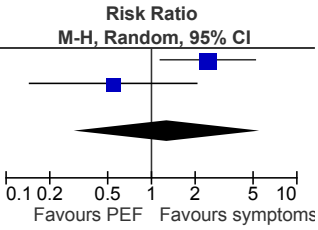


Figure 175: Exacerbations ≥6 months (no. of OCS courses)

Study or Subgroup	PEF monitoring Mean	SD	Total	Symptom monitoring Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Cote 1997	0.7	1.4	50	0.9	1.3	45	100.0%	-0.20 [-0.74, 0.34]
Total (95% CI)			**50**			**45**	**100.0%**	**-0.20 [-0.74, 0.34]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)

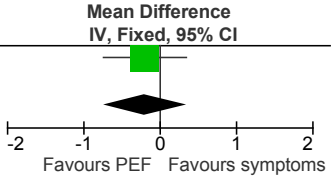


Figure 176: UHU ≥6 months (total asthma-related health care utilisation)

Study or Subgroup	PEF monitoring Mean	SD	Total	Symptom monitoring Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Buist 2006	1.39	1.98	148	1.5	2.23	146	100.0%	-0.11 [-0.59, 0.37]
Total (95% CI)			**148**			**146**	**100.0%**	**-0.11 [-0.59, 0.37]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)

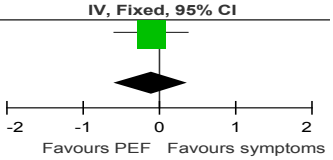


Figure 177: UHU ≥6 months (Hospitalisation)

Study or Subgroup	PEF monitoring Events	PEF monitoring Total	Symptom monitoring Events	Symptom monitoring Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cowie 1997	2	46	2	45	50.3%	0.98 [0.14, 6.65]
Lopez-Vina 2000	2	56	0	44	13.9%	3.95 [0.19, 80.17]
Turner 1998	0	44	1	48	35.8%	0.36 [0.02, 8.68]
Total (95% CI)		**146**		**137**	**100.0%**	**1.17 [0.31, 4.43]**
Total events	4		3			

Heterogeneity: Chi² = 1.18, df = 2 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)

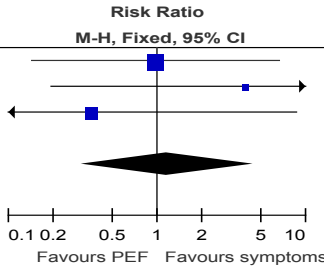


Figure 178: UHU ≥6 months (mean number of hospital admissions)

Study or Subgroup	PEF monitoring Mean	PEF monitoring SD	PEF monitoring Total	Symptom monitoring Mean	Symptom monitoring SD	Symptom monitoring Total	Weight	Mean Difference IV, Fixed, 95% CI
Cote 1997	0.04	0.28	50	0.09	0.27	45	100.0%	-0.05 [-0.16, 0.06]
Total (95% CI)			**50**			**45**	**100.0%**	**-0.05 [-0.16, 0.06]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.89 (P = 0.38)

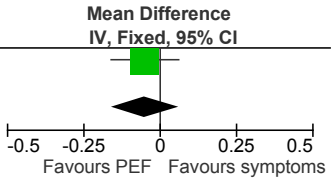


Figure 179: UHU ≥6 months (mean number of days of hospitalisation)

Study or Subgroup	PEF monitoring Mean	PEF monitoring SD	PEF monitoring Total	Symptom monitoring Mean	Symptom monitoring SD	Symptom monitoring Total	Weight	Mean Difference IV, Fixed, 95% CI
Adams 2001	0.07	0.3	48	0.1	0.5	40	100.0%	-0.03 [-0.21, 0.15]
Total (95% CI)			**48**			**40**	**100.0%**	**-0.03 [-0.21, 0.15]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)

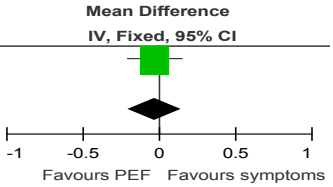


Figure 180: UHU ≥6 months (ED visits)

Study or Subgroup	PEF monitoring Events	PEF monitoring Total	Symptom monitoring Events	Symptom monitoring Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lopez-Vina 2000	3	56	0	44	22.6%	5.53 [0.29, 104.25]
Turner 1998	6	44	2	48	77.4%	3.27 [0.70, 15.38]
Total (95% CI)		**100**		**92**	**100.0%**	**3.78 [0.96, 14.93]**
Total events	9		2			

Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 1.90 (P = 0.06)

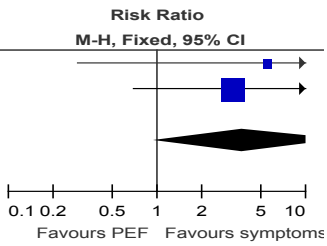


Figure 181: UHU ≥6 months (mean number of ED visits)

Study or Subgroup	PEF monitoring Mean	PEF monitoring SD	PEF monitoring Total	Symptom monitoring Mean	Symptom monitoring SD	Symptom monitoring Total	Weight	Mean Difference IV, Fixed, 95% CI
Adams 2001	0.11	0.4	48	0.15	0.4	40	91.3%	-0.04 [-0.21, 0.13]
Cote 1997	0.7	1.4	50	0.7	1.3	45	8.7%	0.00 [-0.54, 0.54]
Total (95% CI)			**98**			**85**	**100.0%**	**-0.04 [-0.20, 0.12]**

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.45 (P = 0.66)

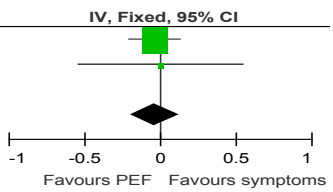


Figure 182: UHU ≥6 months (unscheduled doctors visits)

Study or Subgroup	PEF monitoring Events	PEF monitoring Total	Symptom monitoring Events	Symptom monitoring Total	Weight	Risk Ratio M-H, Random, 95% CI
Cowie 1997	5	46	14	45	47.2%	0.35 [0.14, 0.89]
Turner 1998	17	44	12	48	52.8%	1.55 [0.84, 2.86]
Total (95% CI)		**90**		**93**	**100.0%**	**0.77 [0.18, 3.34]**
Total events	22		26			

Heterogeneity: Tau² = 0.97; Chi² = 6.95, df = 1 (P = 0.008); I² = 86%
Test for overall effect: Z = 0.35 (P = 0.72)

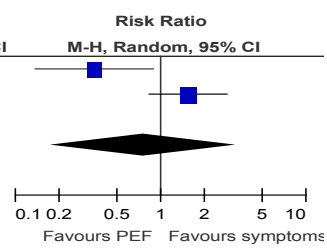


Figure 183: Rescue medications ≥6 months (no. of patients requiring nebulised salbutamol)

Study or Subgroup	PEF monitoring Events	PEF monitoring Total	Symptom monitoring Events	Symptom monitoring Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Charlton 1990	3	28	2	37	100.0%	1.98 [0.35, 11.08]
Total (95% CI)		**28**		**37**	**100.0%**	**1.98 [0.35, 11.08]**
Total events	3		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.78 (P = 0.44)

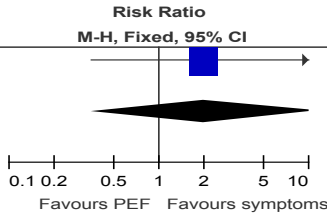


Figure 184: FEV1 L ≥6 months

Study or Subgroup	PEF monitoring Mean	PEF monitoring SD	PEF monitoring Total	Symptom monitoring Mean	Symptom monitoring SD	Symptom monitoring Total	Weight	Mean Difference IV, Fixed, 95% CI
Adams 2001	2.45	0.82	48	2.71	0.86	40	100.0%	-0.26 [-0.61, 0.09]
Total (95% CI)			**48**			**40**	**100.0%**	**-0.26 [-0.61, 0.09]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.44 (P = 0.15)

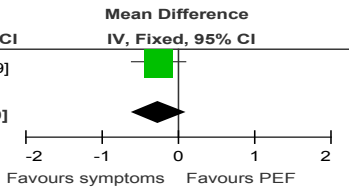


Figure 185: FEV1 % ≥6 months

Study or Subgroup	PEF monitoring Mean	PEF monitoring SD	PEF monitoring Total	Symptom monitoring Mean	Symptom monitoring SD	Symptom monitoring Total	Weight	Mean Difference IV, Fixed, 95% CI
Kaya 2009	87.74	19.02	31	87.35	21.25	32	1.0%	0.39 [-9.56, 10.34]
Lopez-Vina 2000	80.9	2.3	56	80.8	2.8	44	99.0%	0.10 [-0.92, 1.12]
Total (95% CI)			**87**			**76**	**100.0%**	**0.10 [-0.92, 1.12]**

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)

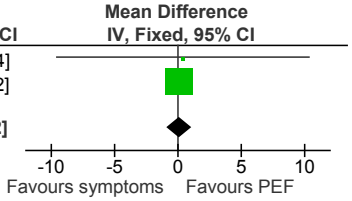


Figure 186: PEF % ≥6 months

Study or Subgroup	PEF monitoring Mean	PEF monitoring SD	PEF monitoring Total	Symptom monitoring Mean	Symptom monitoring SD	Symptom monitoring Total	Weight	Mean Difference IV, Fixed, 95% CI
Kaya 2009	84.93	14.32	31	79.62	14.92	32	100.0%	5.31 [-1.91, 12.53]
Total (95% CI)			**31**			**32**	**100.0%**	**5.31 [-1.91, 12.53]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.44 (P = 0.15)

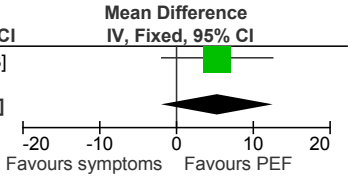


Figure 187: Time off work ≥6 months (number of patients)

Study or Subgroup	PEF monitoring Events	PEF monitoring Total	Symptom monitoring Events	Symptom monitoring Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lopez-Vina 2000	2	56	0	44	6.8%	3.95 [0.19, 80.17]
Turner 1998	9	44	8	48	93.2%	1.23 [0.52, 2.90]
Total (95% CI)		**100**		**92**	**100.0%**	**1.41 [0.62, 3.21]**
Total events	11		8			

Heterogeneity: Chi² = 0.55, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.82 (P = 0.41)

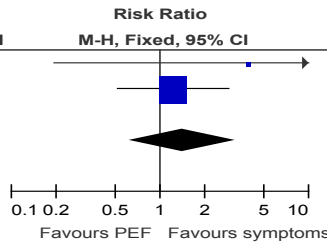
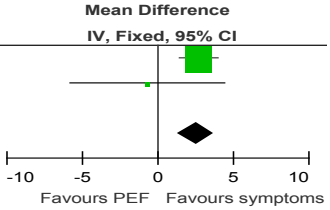


Figure 188: Time off work ≥6 months (mean number of days)

Study or Subgroup	PEF monitoring Mean	PEF monitoring SD	PEF monitoring Total	Symptom monitoring Mean	Symptom monitoring SD	Symptom monitoring Total	Weight	Mean Difference IV, Fixed, 95% CI
Adams 2001	5	1	48	2.3	4	40	94.2%	2.70 [1.43, 3.97]
Cote 1997	2.2	12.7	50	2.9	12.7	45	5.8%	-0.70 [-5.81, 4.41]
Total (95% CI)			**98**			**85**	**100.0%**	**2.50 [1.27, 3.74]**

Heterogeneity: Chi² = 1.60, df = 1 (P = 0.21); I² = 37%
Test for overall effect: Z = 3.97 (P < 0.0001)



1

J.16.1.2 Children: Monitoring PEF versus symptom monitoring

Figure 189: Exacerbations <6 months (OCS)

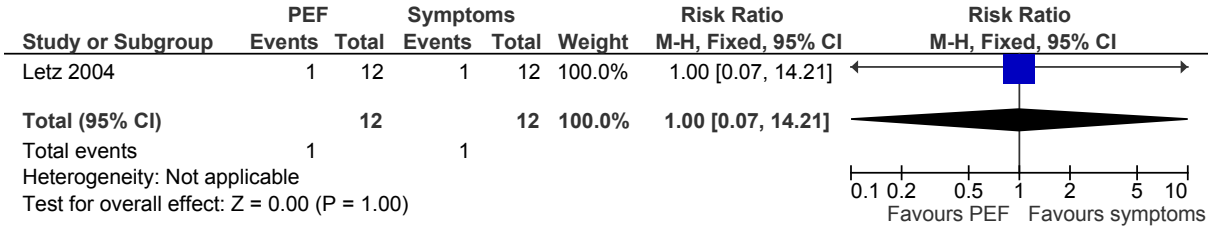


Figure 190: Exacerbations ≥6 months (OCS)

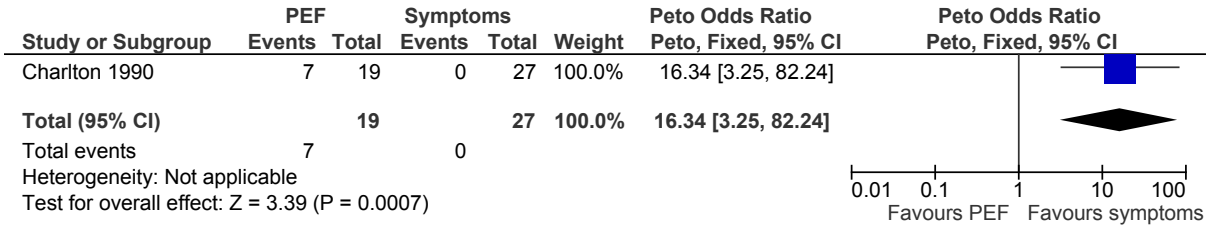


Figure 191: UHU <6 months (hospitalisation)

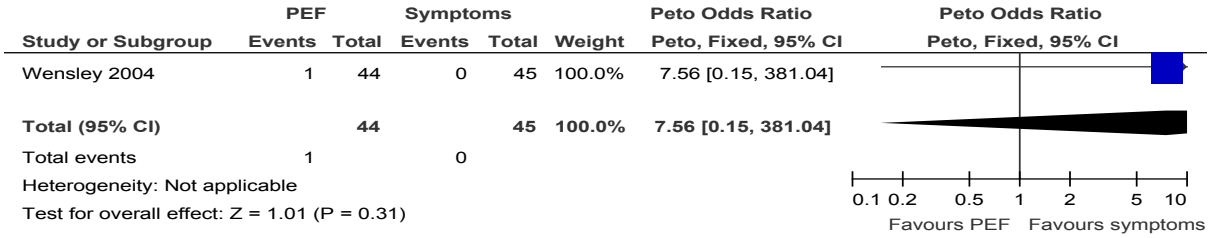


Figure 192: UHU <6 months (attendance at A&E)

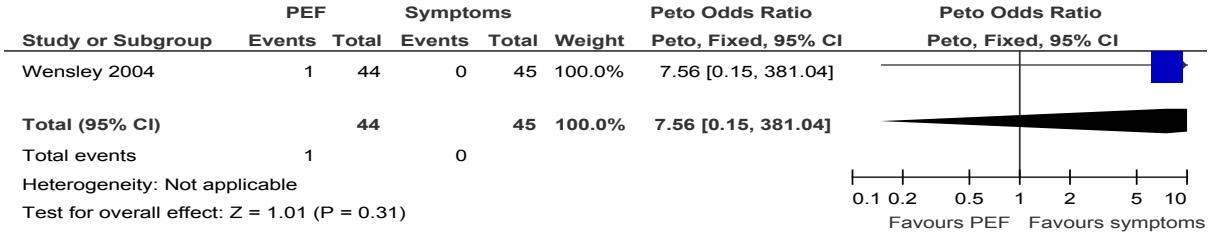


Figure 193: UHU <6 months (emergency GP visits)

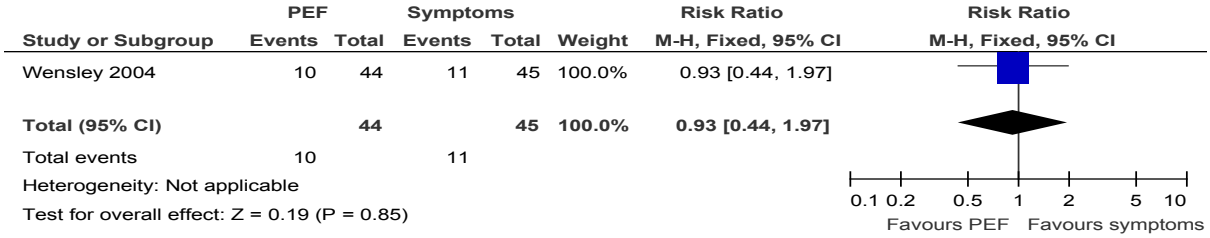


Figure 194: Rescue medications ≥6 months (no. of patients requiring nebulised salbutamol)

Study or Subgroup	PEF Events	PEF Total	Symptoms Events	Symptoms Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Charlton 1990	2	17	0	27	100.0%	14.15 [0.79, 252.10]
Total (95% CI)		**17**		**27**	**100.0%**	**14.15 [0.79, 252.10]**
Total events	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.80 (P = 0.07)

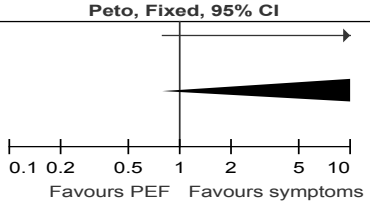


Figure 195: FEV1 % <6 months

Study or Subgroup	PEF Mean	PEF SD	PEF Total	Symptoms Mean	Symptoms SD	Symptoms Total	Weight	Mean Difference IV, Fixed, 95% CI
Wensley 2004	87.3	1.33	44	86.9	1.54	45	99.4%	0.40 [-0.20, 1.00]
Yoos 2002	88	20.6	57	90	21	56	0.6%	-2.00 [-9.67, 5.67]
Total (95% CI)			**101**			**101**	**100.0%**	**0.39 [-0.21, 0.98]**

Heterogeneity: Chi² = 0.37, df = 1 (P = 0.54); I² = 0%
Test for overall effect: Z = 1.27 (P = 0.20)

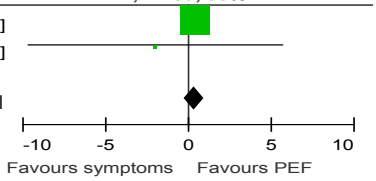


Figure 196: PEF % L/min <6 months

Study or Subgroup	PEF Mean	PEF SD	PEF Total	Symptoms Mean	Symptoms SD	Symptoms Total	Weight	Mean Difference IV, Fixed, 95% CI
Wensley 2004	83.4	1.39	44	80.6	1.74	45	100.0%	2.80 [2.15, 3.45]
Total (95% CI)			**44**			**45**	**100.0%**	**2.80 [2.15, 3.45]**

Heterogeneity: Not applicable
Test for overall effect: Z = 8.40 (P < 0.00001)

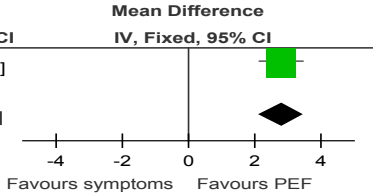
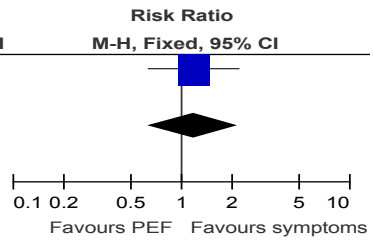


Figure 197: Time off school <6months (number of patients)

Study or Subgroup	PEF Events	PEF Total	Symptoms Events	Symptoms Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Wensley 2004	15	44	13	45	100.0%	1.18 [0.64, 2.18]
Total (95% CI)		**44**		**45**	**100.0%**	**1.18 [0.64, 2.18]**
Total events	15		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.53 (P = 0.60)



J.17 Monitoring: FeNO

J.17.1.1 Adults – Unscheduled healthcare utilisation

Figure 198: FeNO versus Conventional Monitoring in Adults, UHU – ED visit [≥6 months]

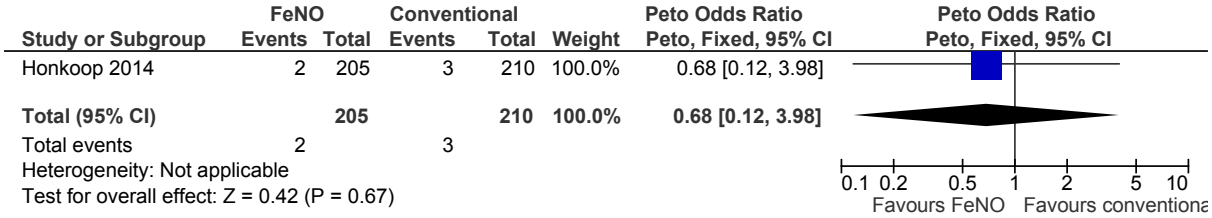
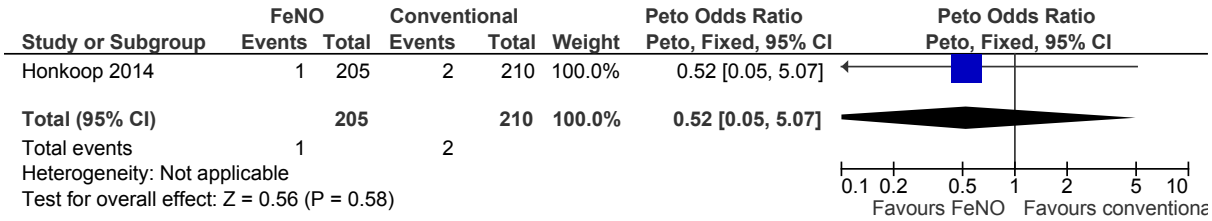


Figure 199: FeNO versus Conventional Monitoring in Adults, UHU - hospitalisation [≥6 months]



J.17.1.2 Adults - Exacerbation

Figure 200: FeNO versus Conventional Monitoring in Adults, exacerbation [≥6 months]

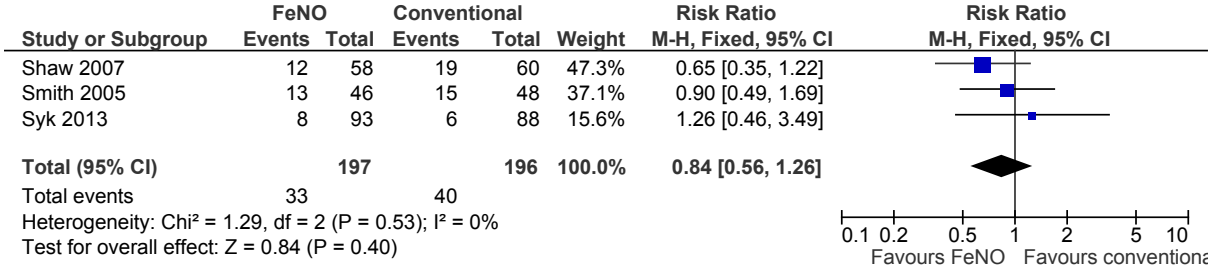


Figure 201: FeNO versus Conventional Monitoring in Adults, exacerbation [≥6 months]

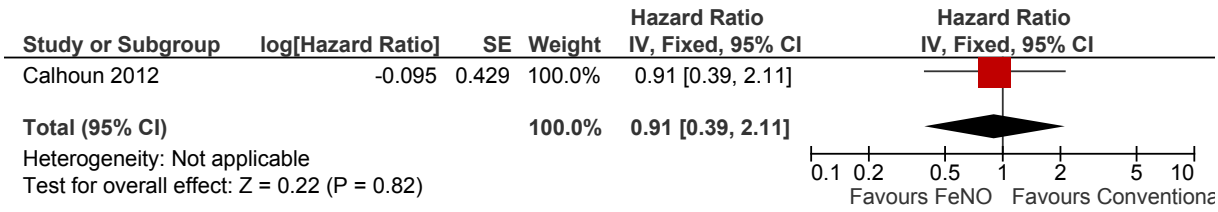
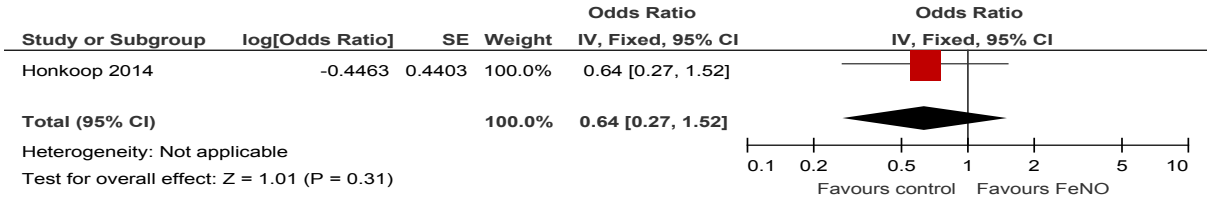
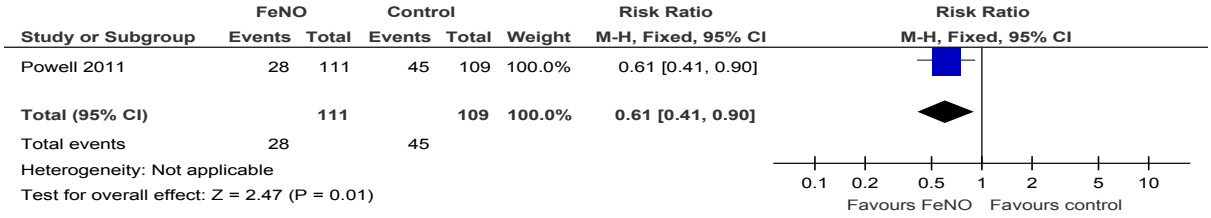


Figure 202: FeNO versus Conventional Monitoring in Adults, exacerbation [≥6 months]



1

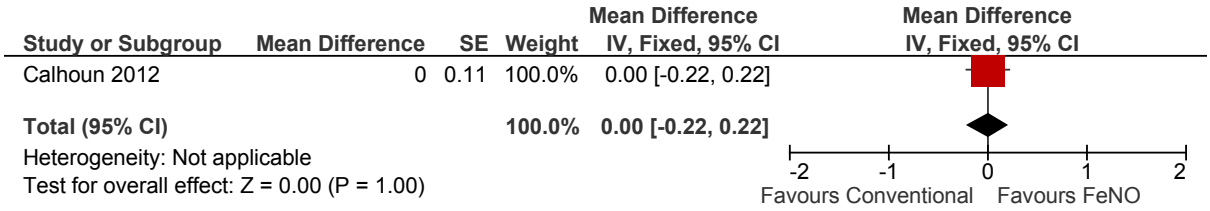
Figure 203: FeNO versus Conventional Monitoring in Adults, exacerbation-mixed [<6 months]



2

3 **J.17.1.3 Adults - Quality of Life**

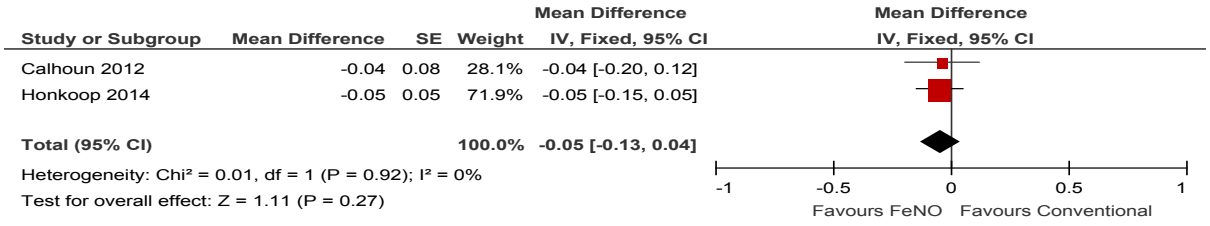
Figure 204: FeNO versus Conventional Monitoring in Adults, quality of life (AQLQ) [≥6 months]



4

5 **J.17.1.4 Adults - Asthma Control Questionnaire**

Figure 205: FeNO versus Conventional Monitoring in Adults, asthma control questionnaire (ACQ) [≥6 months]



6 **Figure 206: FeNO versus Conventional Monitoring in Adults, asthma control questionnaire (ACQ,**
7 **clinically important improvement, ≥0.5) [≥6 months]**

8

9

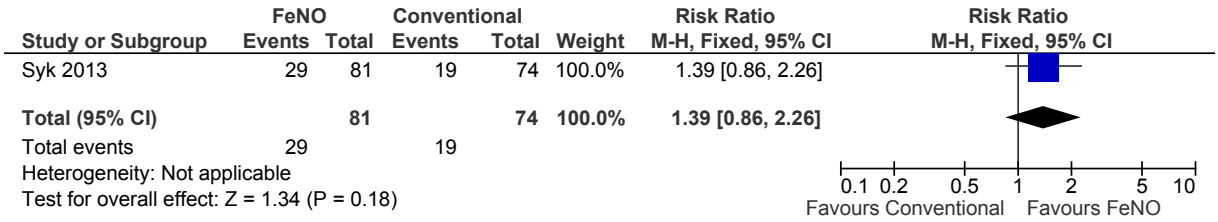


Figure 207: FeNO versus Conventional Monitoring in Adults, asthma control questionnaire (ACQ, mean overall) [<6 months]

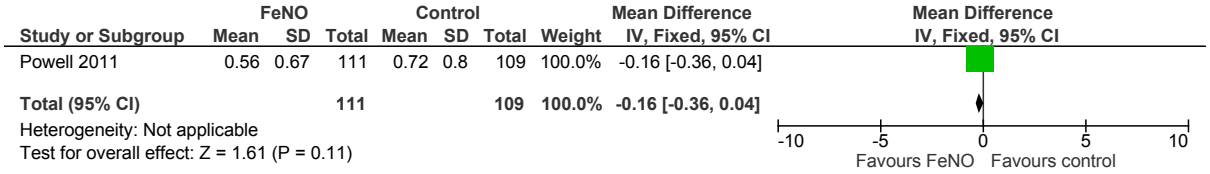


Figure 208: FeNO versus Conventional Monitoring in Adults, asthma control questionnaire (ACQ, mean at exacerbation) [<6 months]

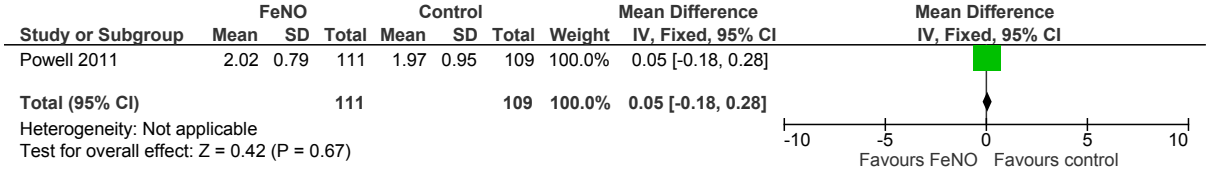
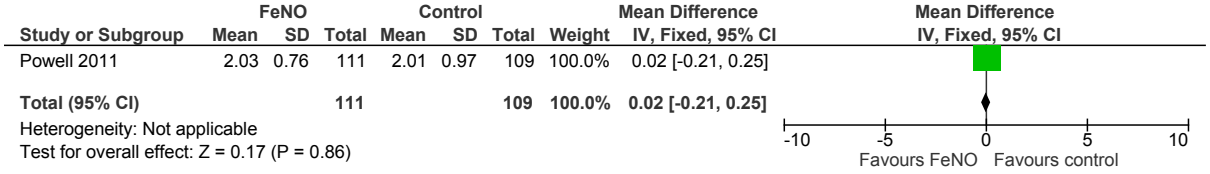


Figure 209: FeNO versus Conventional Monitoring in Adults, asthma control questionnaire (ACQ, mean at unscheduled doctor visits) [< 6 months]



J.17.1.5 Adults - Lung Function

Figure 210: FeNO versus Conventional Monitoring in Adults, lung function (FEV1, litres) [≥6 months]

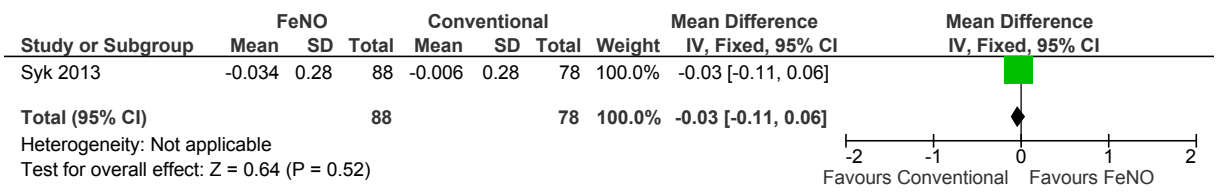


Figure 211: FeNO versus Conventional Monitoring in Adults, lung function (FEV1, %) [≥6 months]

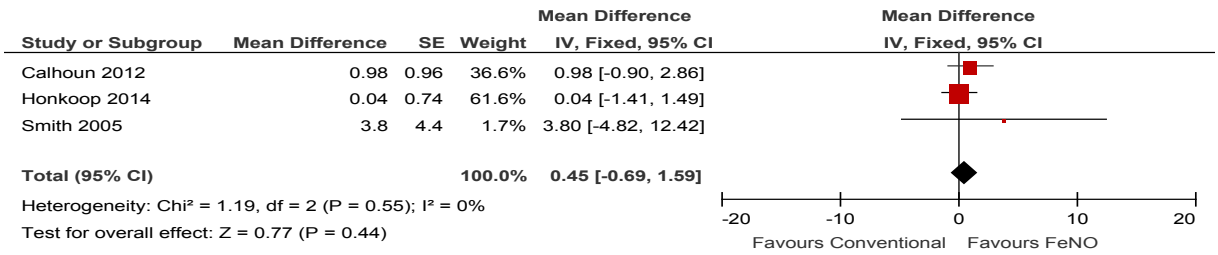


Figure 212: FeNO versus Conventional Monitoring in Adults, lung function (PEF am, L/min) [≥6 months]

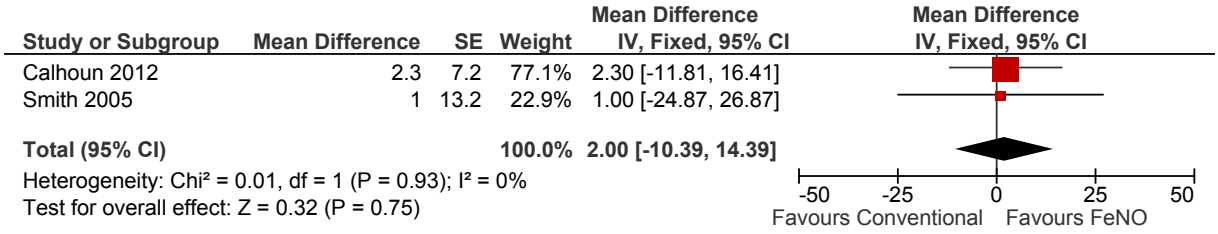
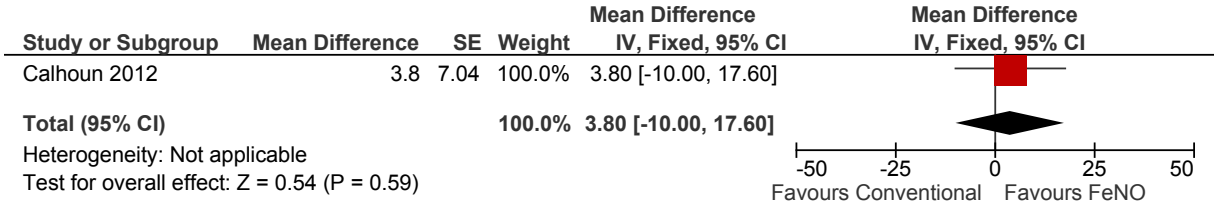
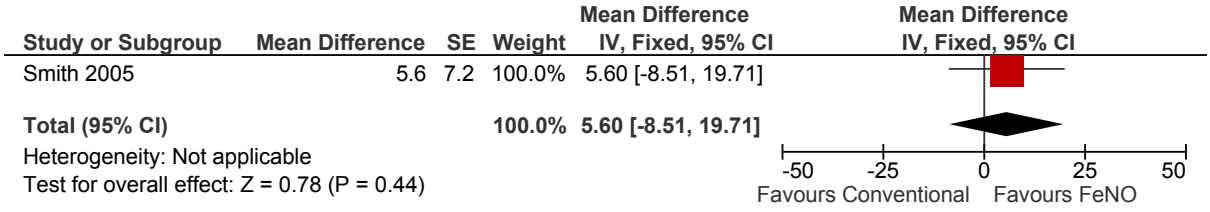


Figure 213: FeNO versus Conventional Monitoring in Adults, lung function (PEF pm, L/min) [<6 months]



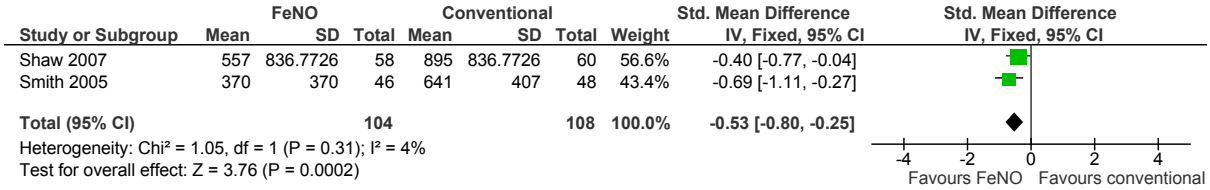
J.17.1.6 Adults - Symptoms

Figure 214: FeNO versus Conventional Monitoring in Adults, % symptom free days [≥6 months]



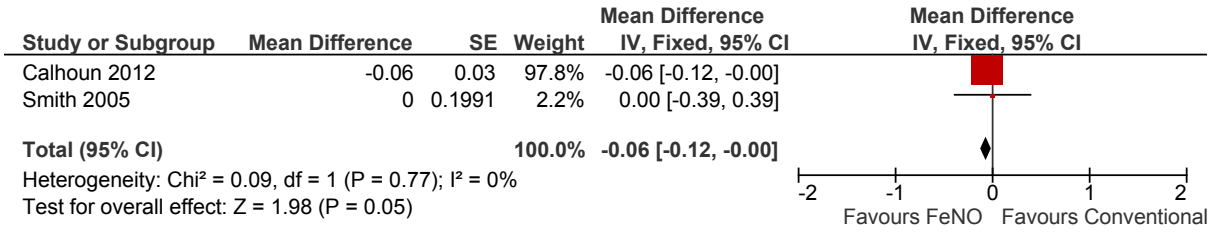
J.17.1.7 Adults - Dose of Regular Therapy

Figure 215: FeNO versus Conventional Monitoring in Adults, dose of regular therapy (ICS use, fluticasone dose) [≥6 months]



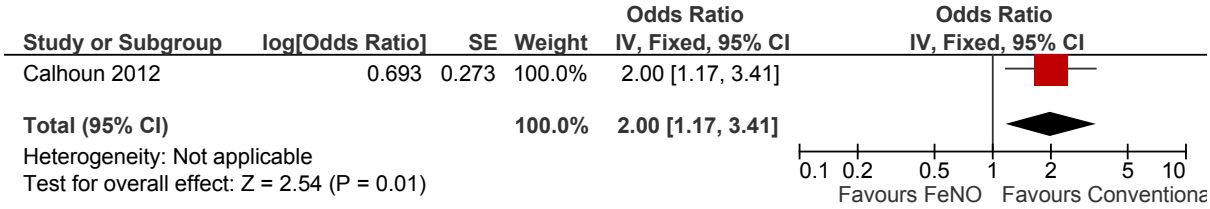
J.17.1.8 Adults - Rescue Medication

Figure 216: FeNO versus Conventional Monitoring in Adults, rescue medication (puffs/day) [≥6 months]



J.17.1.9 Adults - Time off school or work

Figure 217: FeNO versus Conventional Monitoring in Adults, time off (missing days off school or work, number of participants) [≥6 months]



J.17.1.10 Children – Unscheduled Healthcare Utilisation

Figure 218: FeNO versus Conventional Monitoring in Children, unscheduled healthcare utilisation (unscheduled visits) [≥6 months]

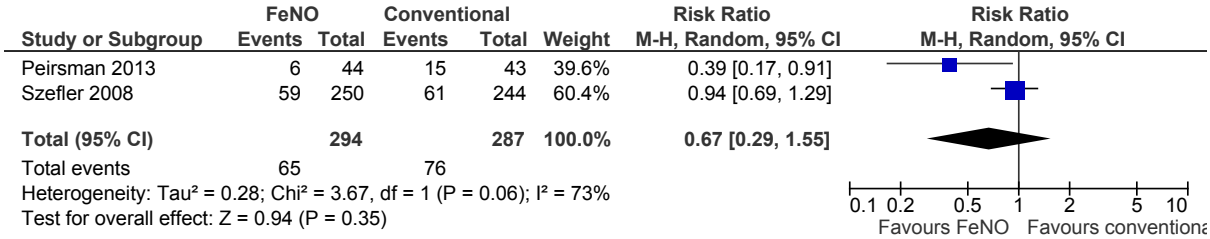


Figure 219: FeNO versus Conventional Monitoring in Children, unscheduled healthcare utilisation (hospitalisation) [≥6 months]

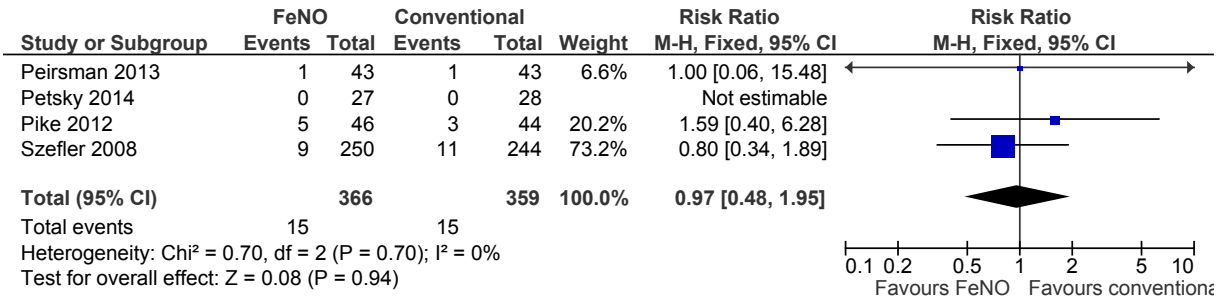
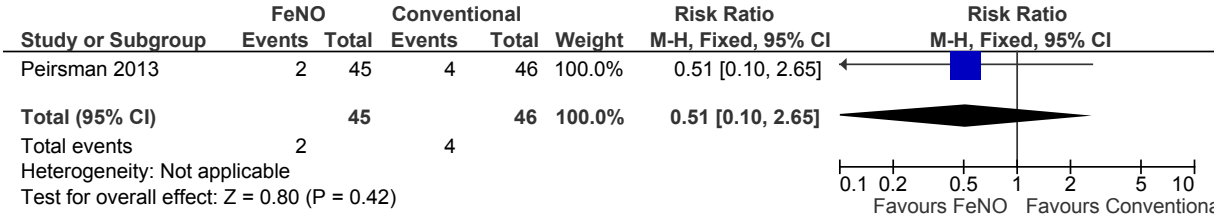
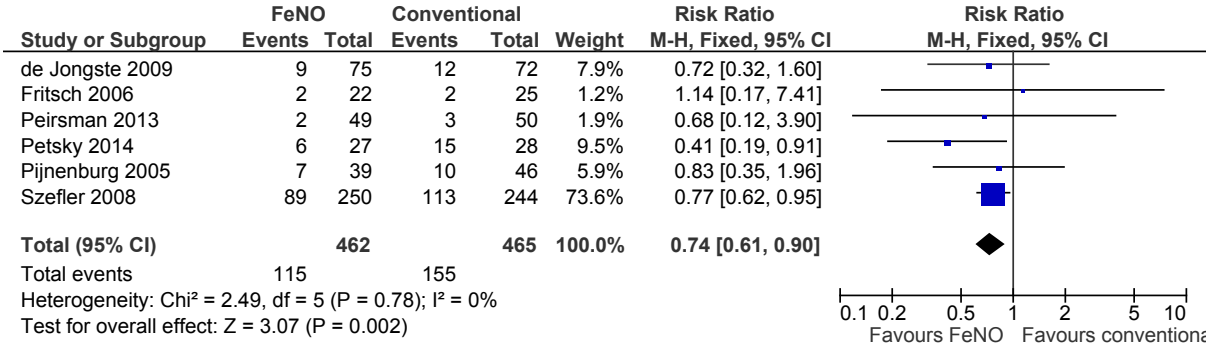


Figure 220: FeNO versus Conventional Monitoring in Children, unscheduled healthcare utilisation (number of children ≥1 emergency room admission) [≥6 months]



J.17.1.11 Children – Exacerbation

Figure 221: FeNO versus Conventional Monitoring in Children, exacerbation (OCS) [≥6 months]



J.17.1.12 Children – Quality of Life

Figure 222: FeNO versus Conventional Monitoring in Children, quality of life (ACT score) [≥6 months]

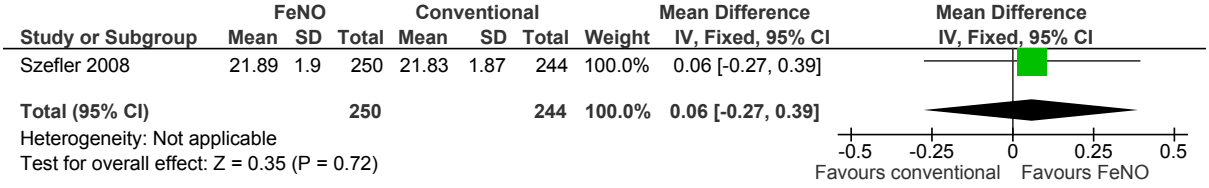
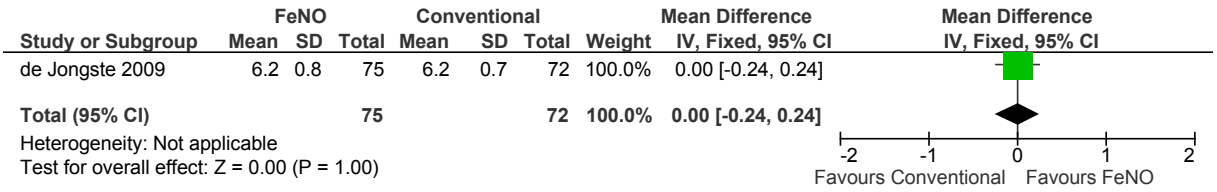
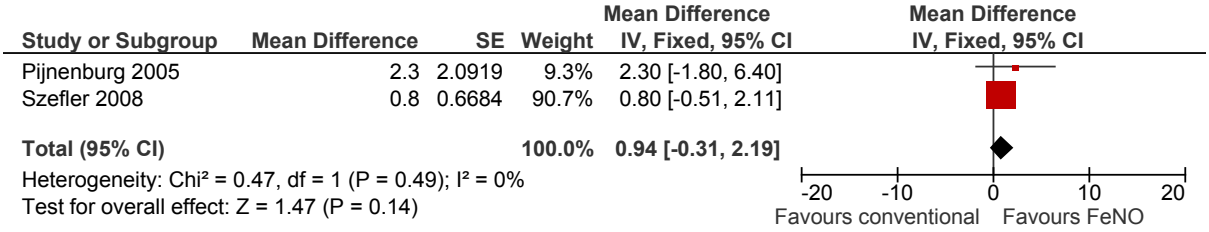


Figure 223: FeNO versus Conventional Monitoring in Children, quality of life (Paediatric Asthma Caregiver Quality of Life Questionnaire) [≥6 months]



J.17.1.13 Children – Lung Function

Figure 224: FeNO versus Conventional Monitoring in Children, lung function (FEV1 % pred) [≥6 months]



J.17.1.14 Children – Symptoms

Figure 225: FeNO versus Conventional Monitoring in Children, symptoms (% symptom free days) [≥6 months]

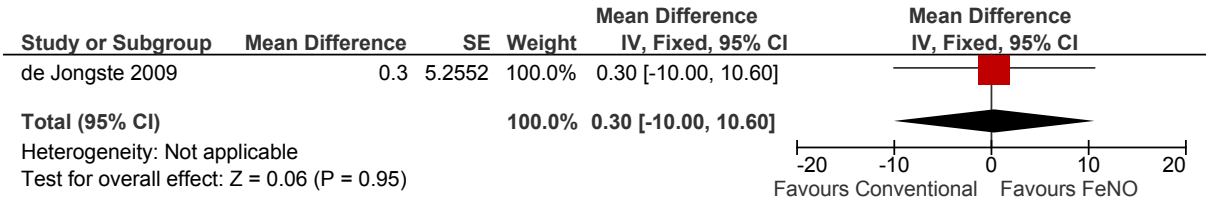
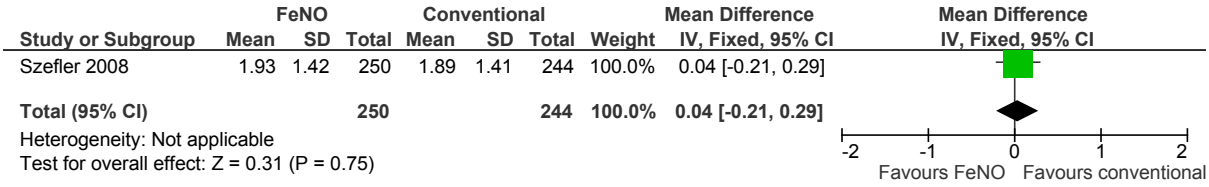


Figure 226: FeNO versus Conventional Monitoring in Children, symptoms (number of symptom days in last 2 weeks) [≥6 months]



1 **J.17.1.15** **Children – Dose of Regular Therapy**

Figure 227: FeNO versus Conventional Monitoring in Children, dose of regular therapy (ICS use, daily dose) [≥6 months]

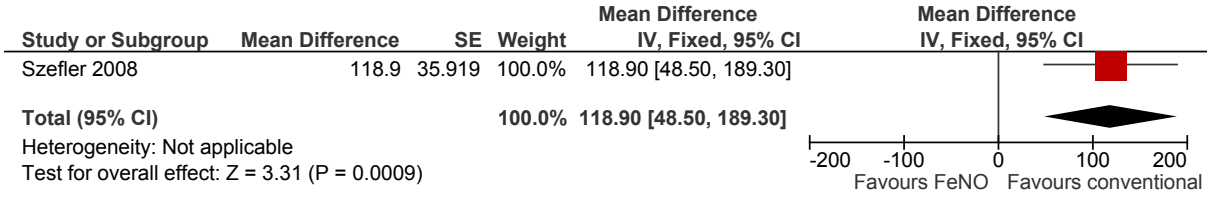
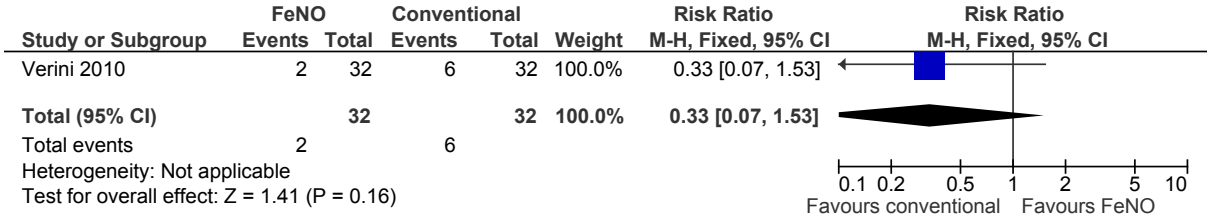
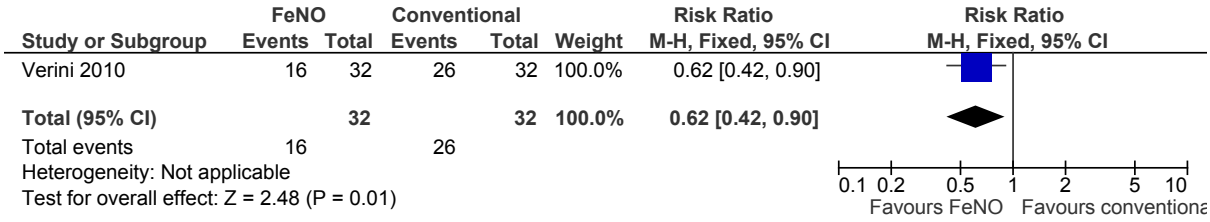


Figure 228: FeNO versus Conventional Monitoring in Children, dose of regular therapy (number of patients not using inhaled corticosteroids or anti-leukotrienes) [≥6 months]



1 J.17.1.16 Children – Rescue Medication

Figure 229: FeNO versus Conventional Monitoring in Children, rescue medication (number of patients needed beta-agonist due to symptoms) [≥6 months]



2 J.17.1.17 Children – Time Off school

Figure 230: FeNO versus Conventional Monitoring in Children, time off (number of days missed in last 2 weeks) [≥6 months]

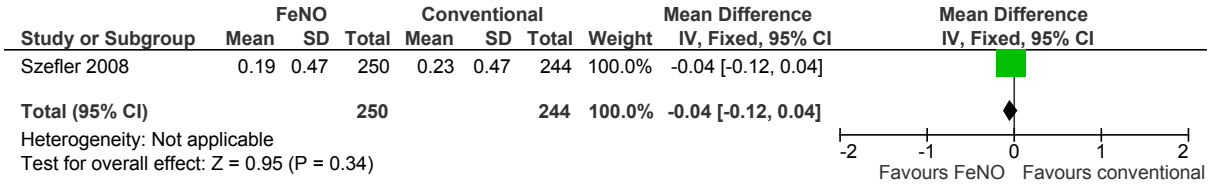
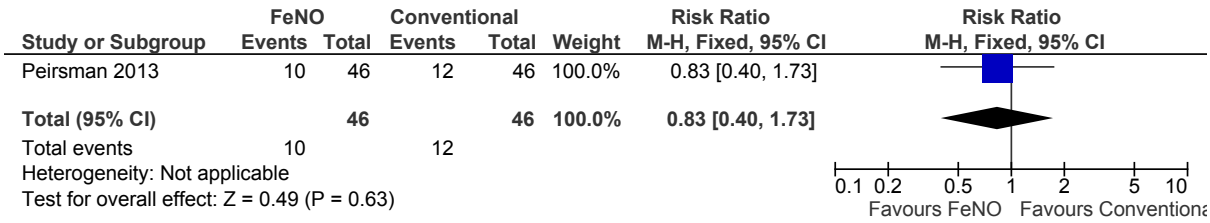


Figure 231: FeNO versus Conventional Monitoring in Children, time off (number of children missed school) [≥6 months]



3 J.18 Monitoring: Challenge tests

4 J.18.1.1 ADULTS Methacholine challenge test versus no challenge test for asthma monitoring

Figure 232: Mortality ≥6 months

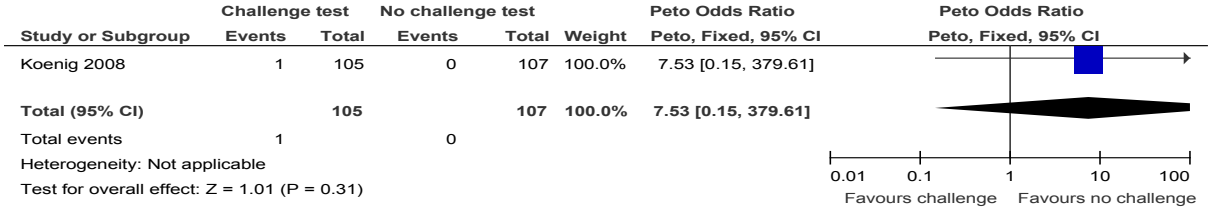


Figure 233: Exacerbations (undefined) ≥6 months

Study or Subgroup	Challenge test Events	Total	No challenge test Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Koenig 2008	22	105	26	107	100.0%	0.86 [0.52, 1.42]
Total (95% CI)		**105**		**107**	**100.0%**	**0.86 [0.52, 1.42]**
Total events	22		26			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)

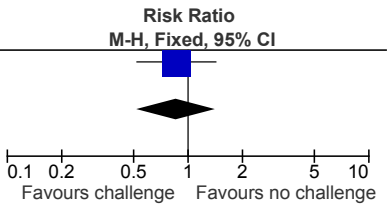


Figure 234: Rescue medications (puffs/day) ≥6 months

Study or Subgroup	Challenge test Mean	SD	Total	No challenge test Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Koenig 2008	-0.8	1.8	105	-0.7	1.8	107	100.0%	-0.10 [-0.58, 0.38]
Total (95% CI)			**105**			**107**	**100.0%**	**-0.10 [-0.58, 0.38]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.40 (P = 0.69)

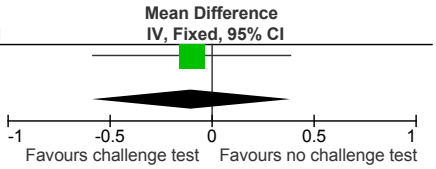


Figure 235: ICS mean daily dose ≥6 months

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
1.6.1 New Subgroup				
Koenig 2008	131.2	24.3	100.0%	131.20 [83.57, 178.83]
Subtotal (95% CI)			**100.0%**	**131.20 [83.57, 178.83]**
Total (95% CI)			**100.0%**	**131.20 [83.57, 178.83]**

Heterogeneity: Not applicable
Test for overall effect: Z = 5.40 (P < 0.00001)
Heterogeneity: Not applicable
Test for overall effect: Z = 5.40 (P < 0.00001)
Test for subgroup differences: Not applicable

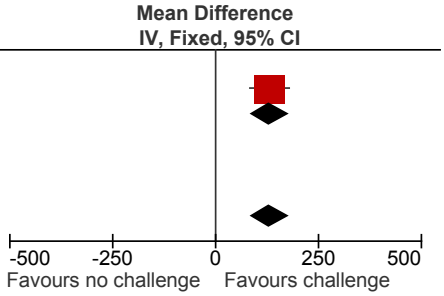


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Figure 236: FEV1 (L or L/year) ≥6 months

Study or Subgroup	Challenge test Mean	SD	Total	No challenge test Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Koenig 2008	0.06	0.51	105	0.11	0.52	107	36.5%	-0.05 [-0.19, 0.09]
Sont 1999	0.078	0.034	32	-0.007	0.036	35	63.5%	0.09 [0.07, 0.10]
Total (95% CI)			**137**			**142**	**100.0%**	**0.04 [-0.09, 0.16]**

Heterogeneity: Tau² = 0.01; Chi² = 3.59, df = 1 (P = 0.06); I² = 72%
Test for overall effect: Z = 0.55 (P = 0.58)

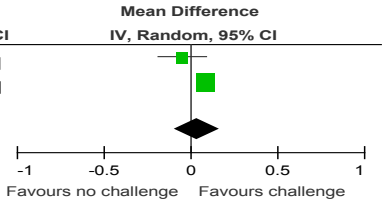


Figure 237: % symptom free days ≥6 months

Study or Subgroup	Challenge test Mean	SD	Total	No challenge test Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Koenig 2008	13	56.2	105	18.1	54.9	107	100.0%	-5.10 [-20.06, 9.86]
Total (95% CI)			**105**			**107**	**100.0%**	**-5.10 [-20.06, 9.86]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)

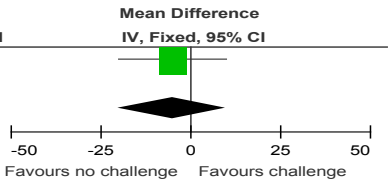


Figure 238: PEF am (L/min) ≥6 months

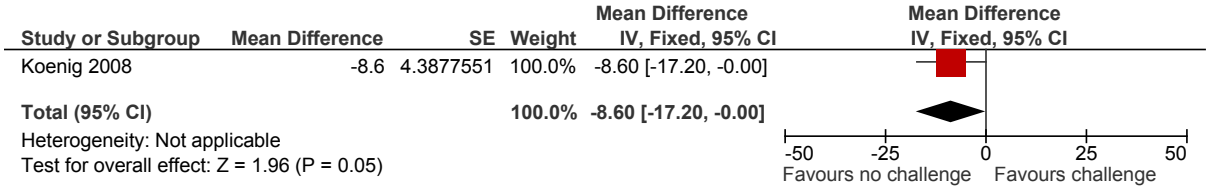
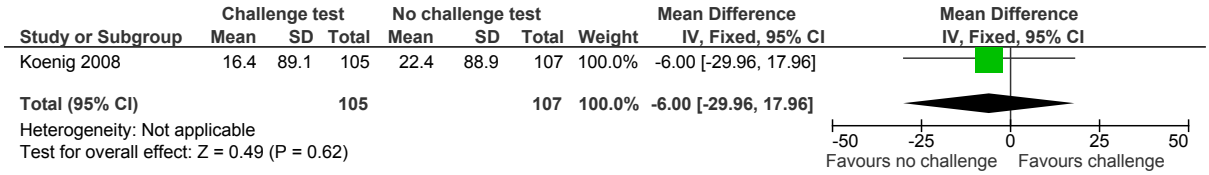


Figure 239: PEF pm (L/min) ≥6 months



1 **J.18.1.2 ADULTS Mannitol challenge test versus no challenge test for asthma monitoring**

Figure 240: QOL (miniAQLQ) ≥6 months

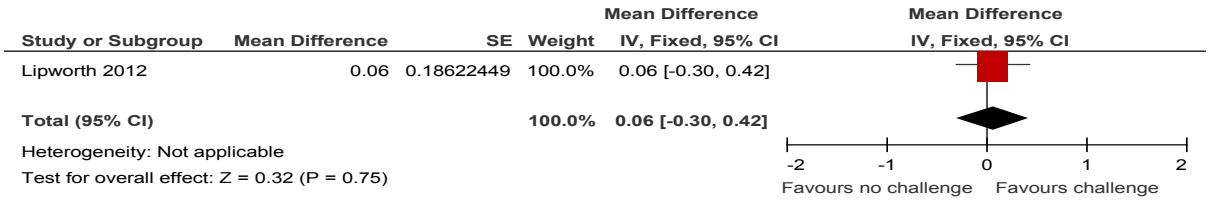


Figure 241: Exacerbations (OCS) ≥6 months

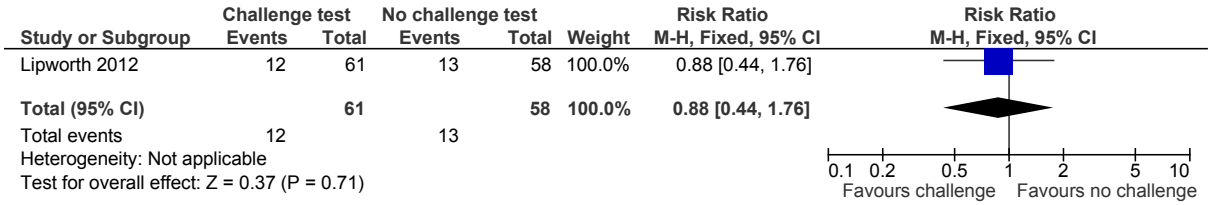
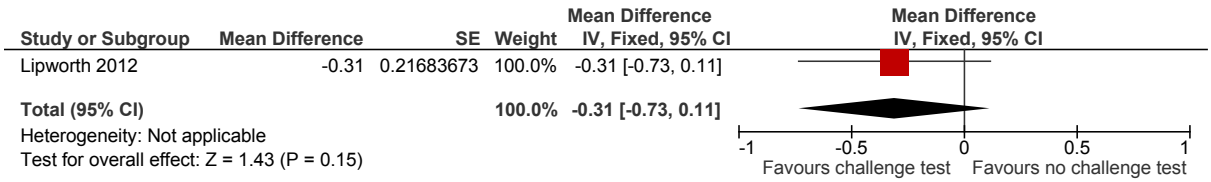


Figure 242: Rescue medications (puffs/day) ≥6 months



2

Figure 243: ICS mean daily dose ≥6 months

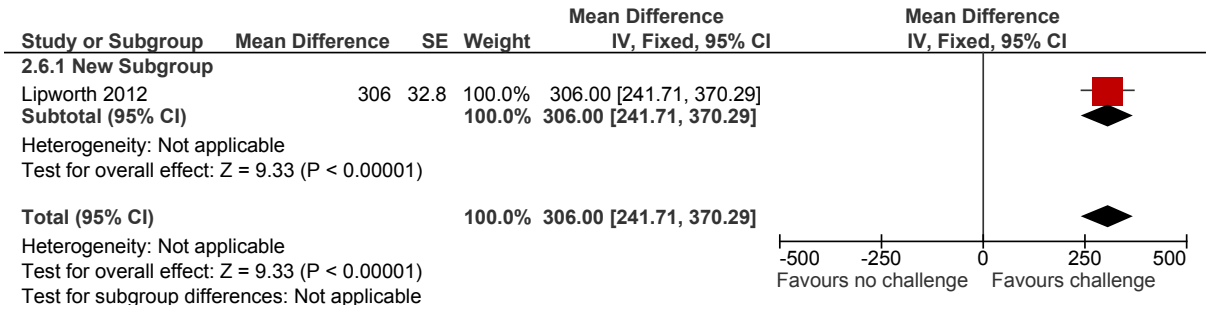


Figure 244: FEV1 (%) ≥6 months

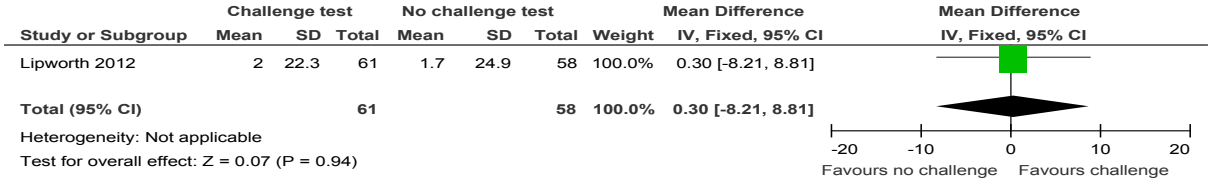


Figure 245: PEF (%) ≥6 months

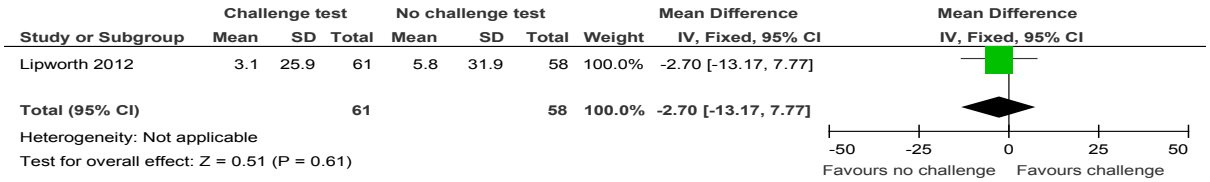
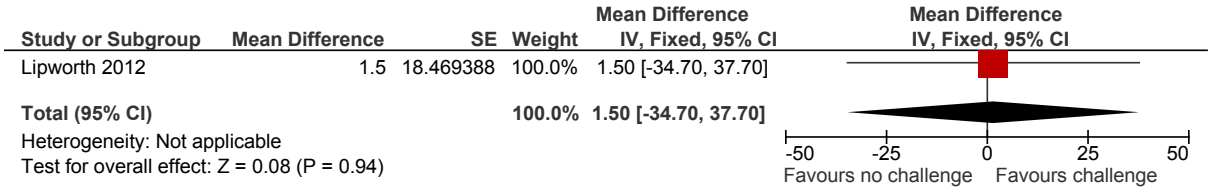


Figure 246: PEF am (L/min) ≥6 months



1 J.18.1.3 CHILDREN Methacholine challenge test versus no challenge test for asthma monitoring

Figure 247: Exacerbations (OCS) ≥6 months

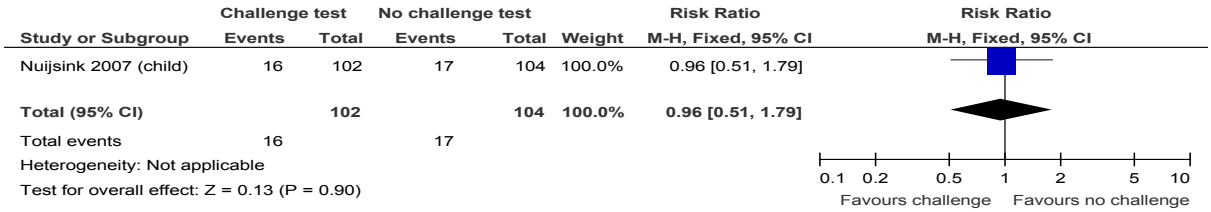


Figure 248: ICS mean daily dose for treatment period ≥6 months

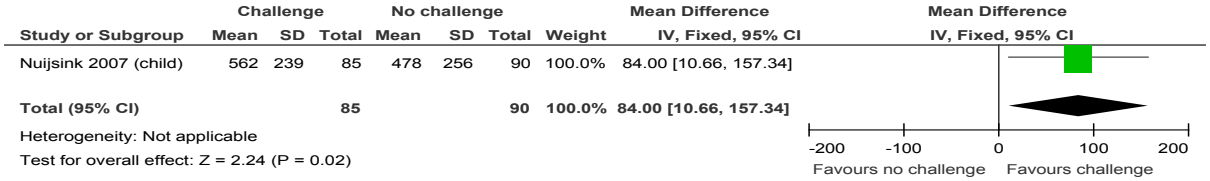


Figure 249: FEV1 (%)≥6 months

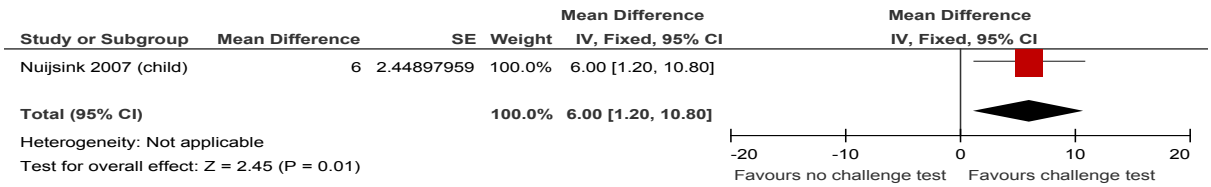
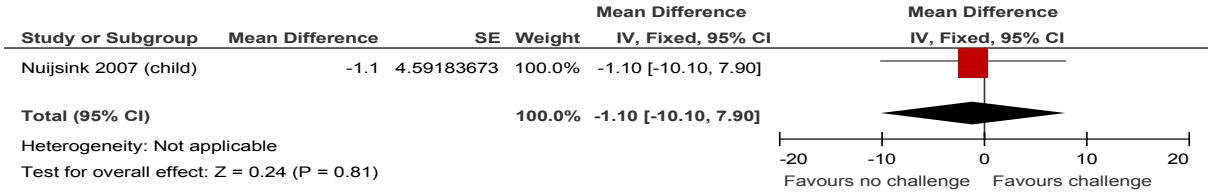


Figure 250: % symptom free days ≥6 months



J.19 Monitoring adherence to treatment

J.19.1.1 Children (5-16 years) with uncontrolled asthma: Monitoring adherence + feedback vs no monitoring

Figure 251: Adherence <6 months (% of prescribed doses measured by the electronic inhaler)

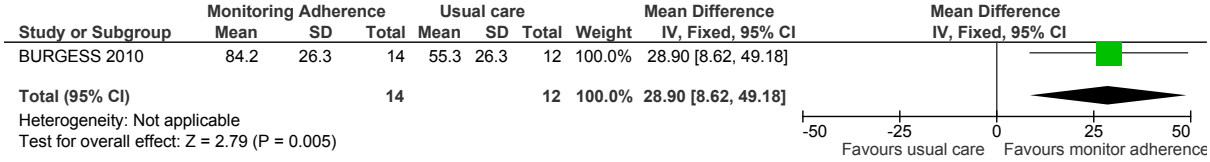


Figure 252: Adherence ≥6 months (number of canister refills, 100% adherence = 3.0)

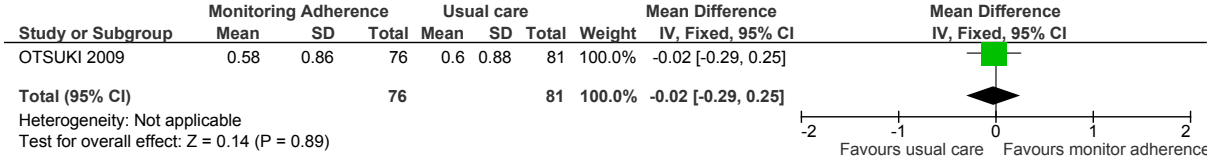


Figure 253: Self-reported adherence ≥6 months

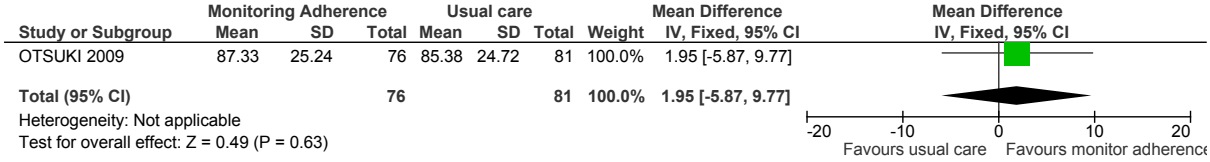


Figure 254: Exacerbation (OCS) <6 months

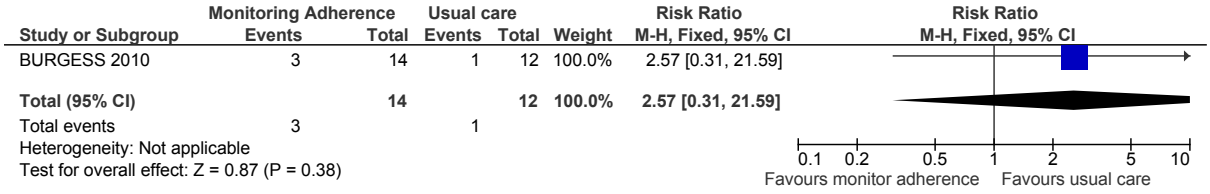


Figure 255: Exacerbation (OCS) ≥6 months (no. of OCS courses in 6 months)

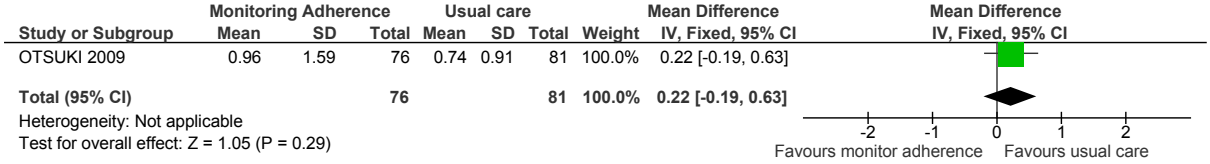


Figure 256: UHU (hospitalisation) ≥6 months (no. of hospitalisations in 6 months)

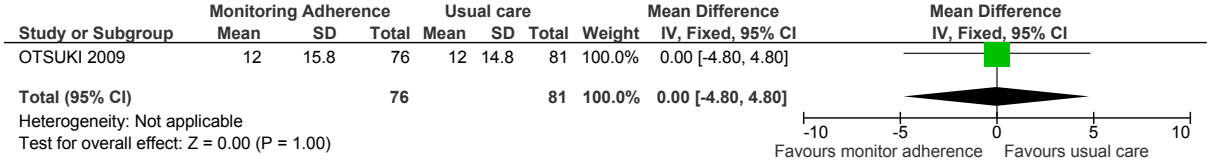
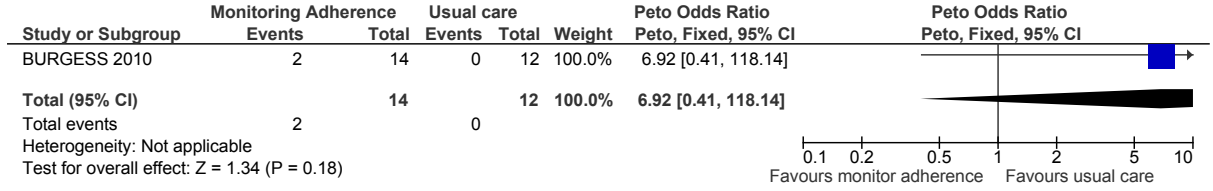


Figure 257: Rescue medication < 6months (reliever medication 3 or more times a week)



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2 **J.19.1.2 Adults (>16 years) overall: Monitoring adherence + feedback vs no monitoring**

Figure 258: Adherence ≥6 months (% adherence to prescription refills in previous 3 months)

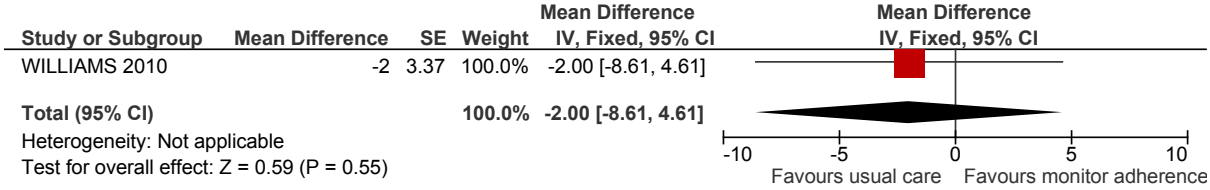


Figure 259: QOL <6 months (AQLQ, range 1-7)

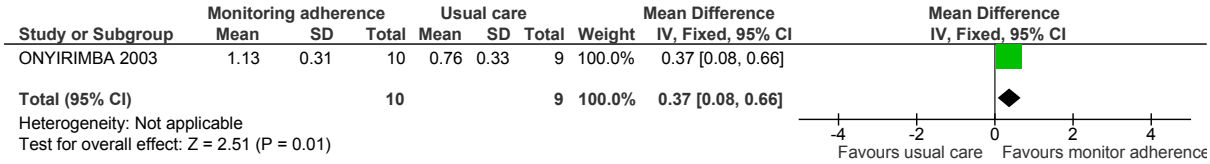


Figure 260: Exacerbation (OCS) ≥6months

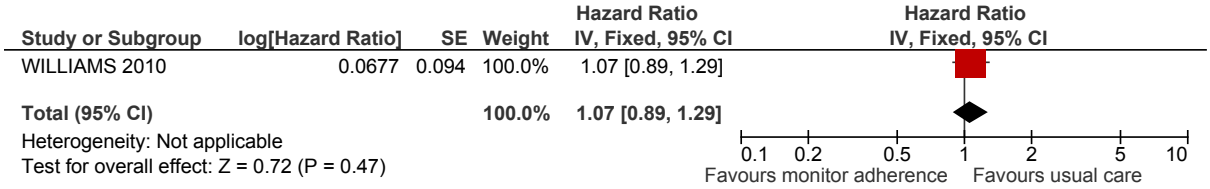


Figure 261: UHU (hospitalisation) ≥6months

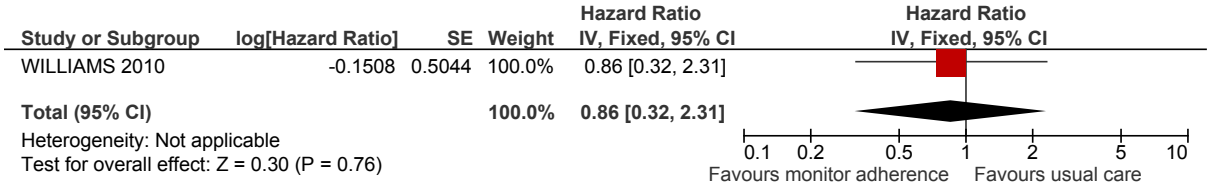


Figure 262: UHU (ED visit) ≥6months

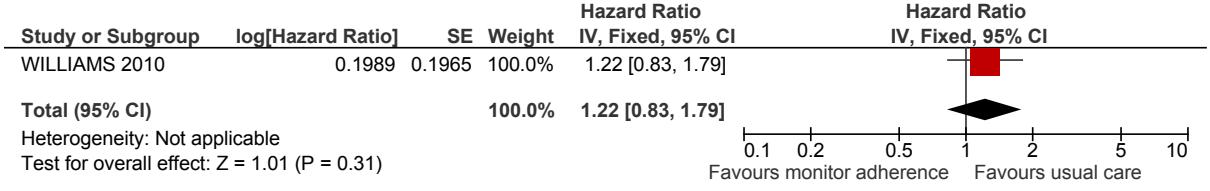
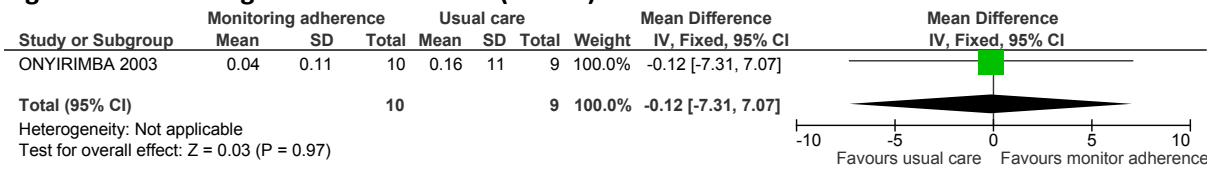


Figure 263: Lung function <6months (FEV1 L)



J.20 Monitoring inhaler technique

J.20.1.1 ADULTS: Monitoring inhaler technique vs no monitoring

Figure 264: Lung function <6 months (PEF Min%Max, higher is less variability)

Study or Subgroup	Monitoring Mean [%]	SD [%]	Total	No monitoring Mean [%]	SD [%]	Total	Weight	Mean Difference IV, Fixed, 95% CI [%]
BASHETI 2007	83.8	8.3	53	77.6	9.2	44	100.0%	6.20 [2.68, 9.72]
Total (95% CI)			**53**			**44**	**100.0%**	**6.20 [2.68, 9.72]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.45 (P = 0.0006)

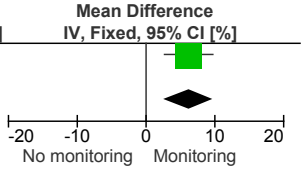


Figure 265: Lung function ≥6 months (PEF Min%Max, higher is less variability)

Study or Subgroup	Monitoring Mean [%]	SD [%]	Total	No monitoring Mean [%]	SD [%]	Total	Weight	Mean Difference IV, Fixed, 95% CI [%]
BASHETI 2007	78.9	9.7	53	74.4	8.9	44	100.0%	4.50 [0.79, 8.21]
Total (95% CI)			**53**			**44**	**100.0%**	**4.50 [0.79, 8.21]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.38 (P = 0.02)

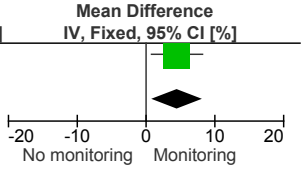


Figure 266: QOL <6 months (Marks AQLQ, 0-10, better indicated by lower values)

Study or Subgroup	Monitoring Mean	SD	Total	No monitoring Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
BASHETI 2007	0.8	0.5	53	1.35	0.6	44	100.0%	-0.55 [-0.77, -0.33]
Total (95% CI)			**53**			**44**	**100.0%**	**-0.55 [-0.77, -0.33]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.84 (P < 0.00001)

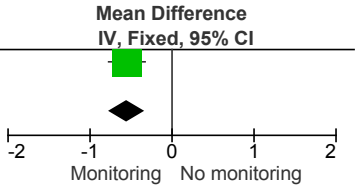
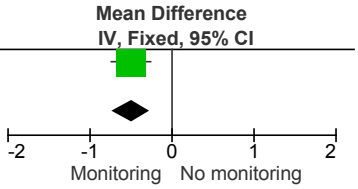


Figure 267: QOL ≥6 months (Marks AQLQ, 0-10, better indicated by lower values)

Study or Subgroup	Monitoring Mean	SD	Total	No monitoring Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
BASHETI 2007	0.8	0.6	53	1.3	0.6	44	100.0%	-0.50 [-0.74, -0.26]
Total (95% CI)			**53**			**44**	**100.0%**	**-0.50 [-0.74, -0.26]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.09 (P < 0.0001)



J.20.1.2 ADULTS: Monitoring (verbal and electronic) vs verbal monitoring only

Figure 268: QOL <6 months (mini AQLQ, 1-7, better indicated by higher values)

Study or Subgroup	Verbal and electronic Mean	SD	Total	Verbal only Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
ALSHOWAIR 2007	4.6	1	36	4.2	1	35	74.6%	0.40 [-0.07, 0.87]
AMMARI 2013	-0.409	1.05	17	-0.748	1.31	17	25.4%	0.34 [-0.46, 1.14]
Total (95% CI)			**53**			**52**	**100.0%**	**0.38 [-0.02, 0.79]**

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.90); I² = 0%
Test for overall effect: Z = 1.88 (P = 0.06)

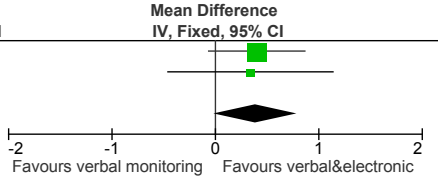


Figure 269: Lung function <6 months (FEV1 L)

Study or Subgroup	Verbal and electronic Mean [L]	SD [L]	Total	Verbal only Mean [L]	SD [L]	Total	Weight	Mean Difference IV, Fixed, 95% CI [L]
ALSHOWAIR 2007	1.93	0.63	36	2.16	0.74	35	100.0%	-0.23 [-0.55, 0.09]
Total (95% CI)			**36**			**35**	**100.0%**	**-0.23 [-0.55, 0.09]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.41 (P = 0.16)

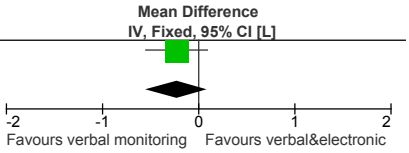
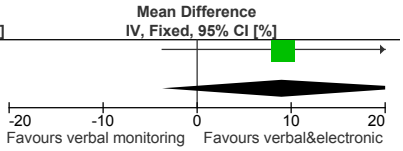


Figure 270: Lung function <6 months (FEV1 % pred)

Study or Subgroup	Verbal and electronic Mean [%]	SD [%]	Total	Verbal only Mean [%]	SD [%]	Total	Weight	Mean Difference IV, Fixed, 95% CI [%]
AMMARI 2013	96.3	17.6	17	87.2	20.4	17	100.0%	9.10 [-3.71, 21.91]
Total (95% CI)			**17**			**17**	**100.0%**	**9.10 [-3.71, 21.91]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.39 (P = 0.16)



J.20.1.3 CHILDREN: Monitoring (verbal and electronic) vs verbal monitoring only

Figure 271: Lung function <6 months (FEV1 % pred)

Study or Subgroup	Verbal and electronic Mean [%]	SD [%]	Total	Verbal only Mean [%]	SD [%]	Total	Weight	Mean Difference IV, Fixed, 95% CI [%]
AMMARI 2013	90.9	14.3	6	94.1	4.8	6	100.0%	-3.20 [-15.27, 8.87]
Total (95% CI)			**6**			**6**	**100.0%**	**-3.20 [-15.27, 8.87]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.52 (P = 0.60)

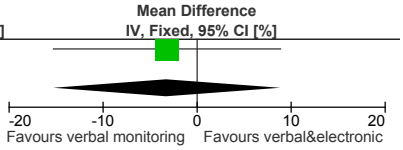
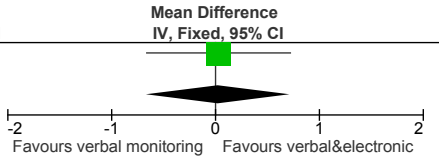


Figure 272: QOL <6 months (PAQLQ, 1-7, better indicated by higher values)

Study or Subgroup	Verbal and electronic Mean	SD	Total	Verbal only Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
AMMARI 2013	-0.362	0.52	6	-0.391	0.69	6	100.0%	0.03 [-0.66, 0.72]
Total (95% CI)			**6**			**6**	**100.0%**	**0.03 [-0.66, 0.72]**

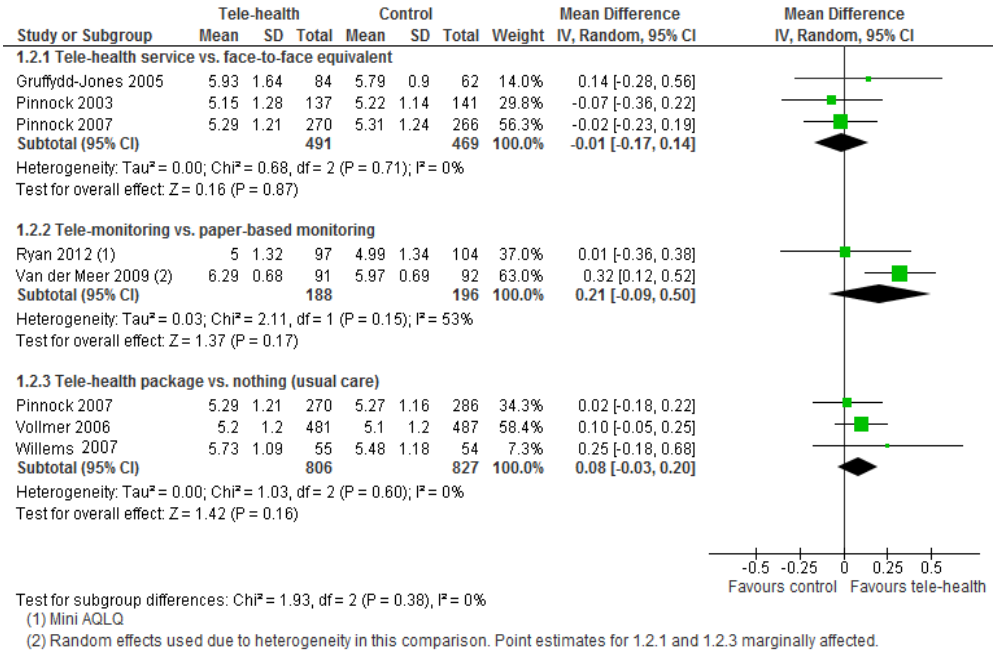
Heterogeneity: Not applicable
Test for overall effect: Z = 0.08 (P = 0.93)



J.21 Monitoring: Tele-healthcare

J.21.1.1 Tele-healthcare for adults >17

Figure 273: Quality of life – Asthma Quality of Life Questionnaire (AQLQ)



(1) Mini AQLQ

(2) Random effects used due to heterogeneity in this comparison. Point estimates for 1.2.1 and 1.2.3 marginally affected.

Figure 274: UHU hospitalisation

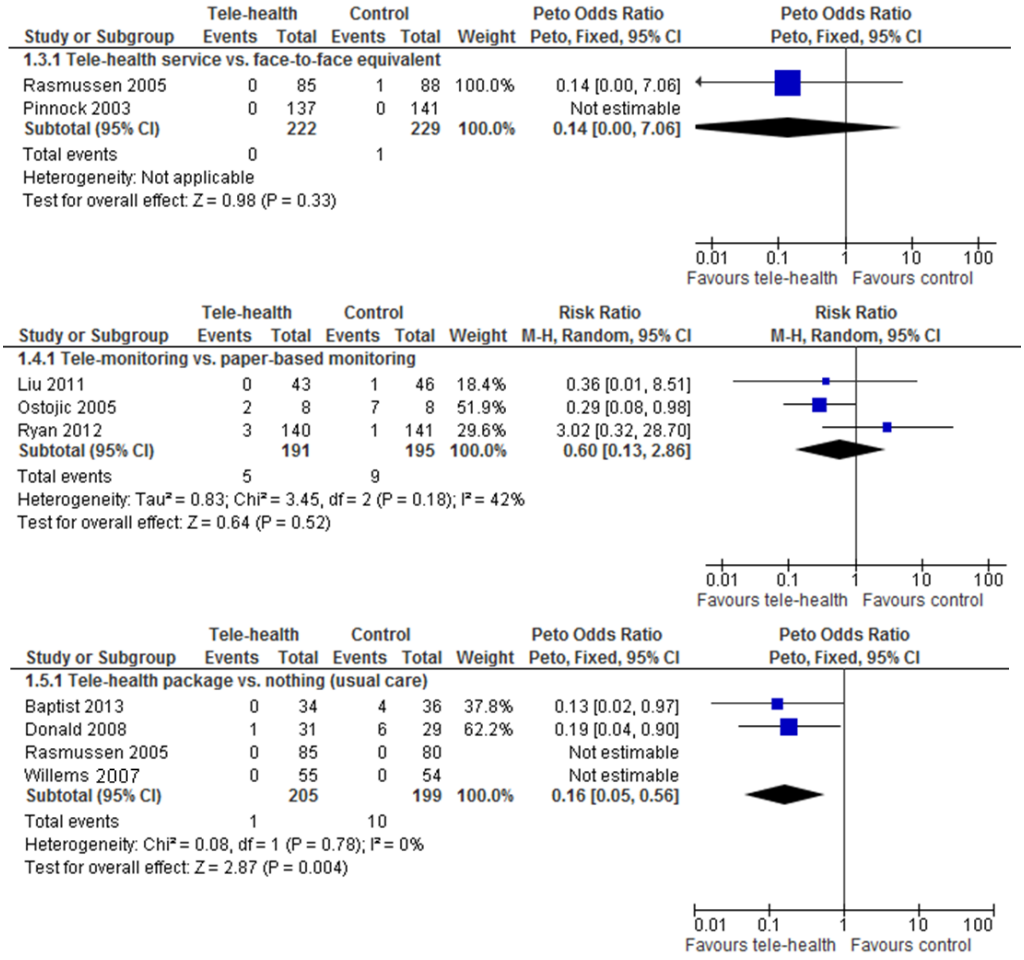


Figure 275: UHU ED visit

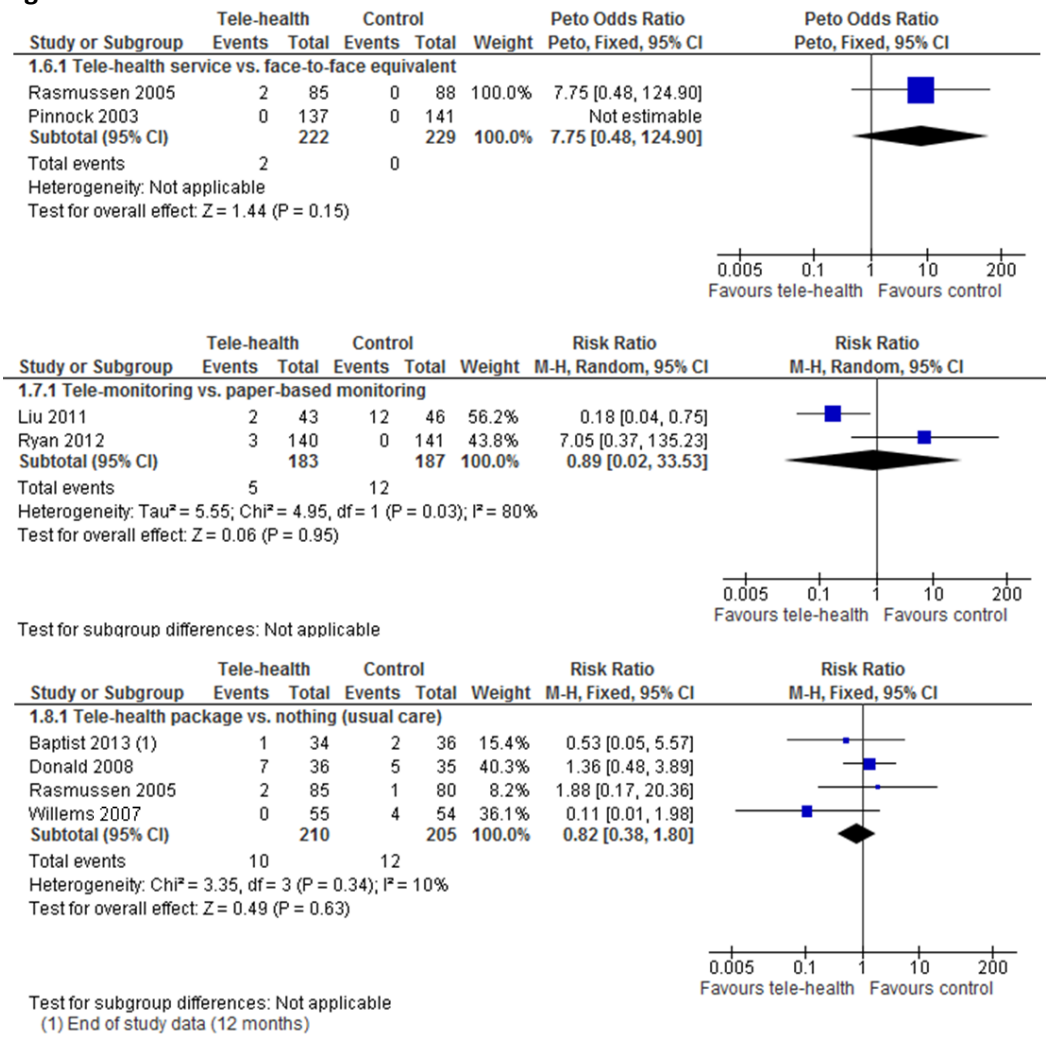


Figure 276: Exacerbations requiring oral steroids

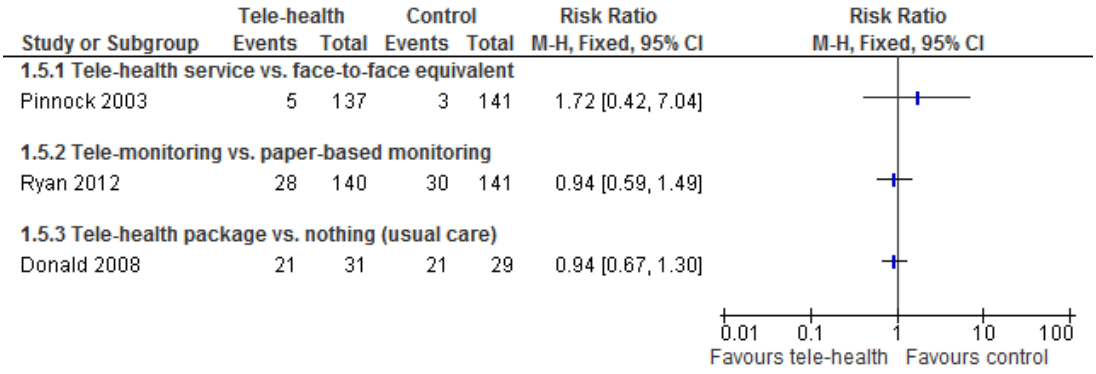
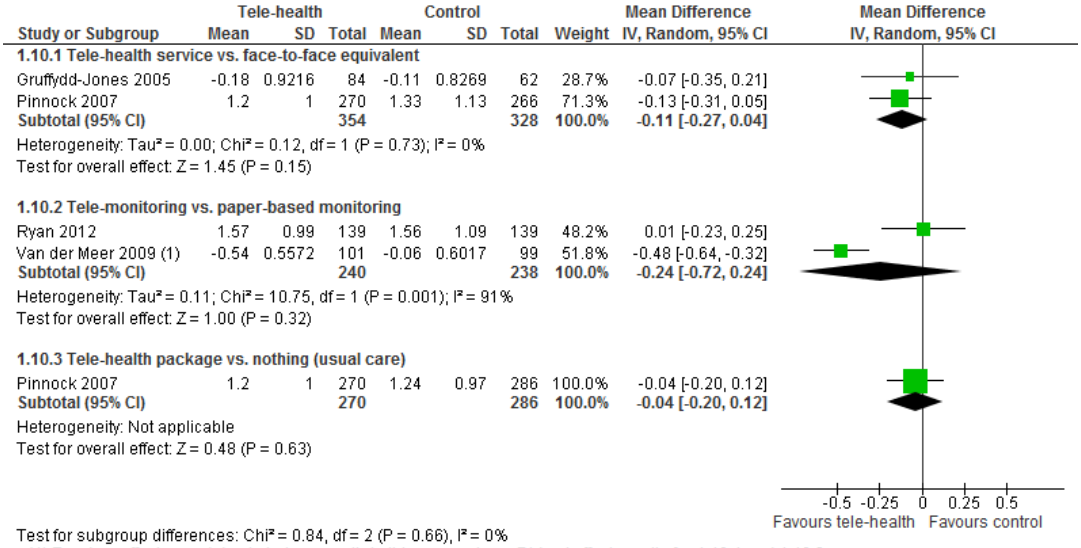
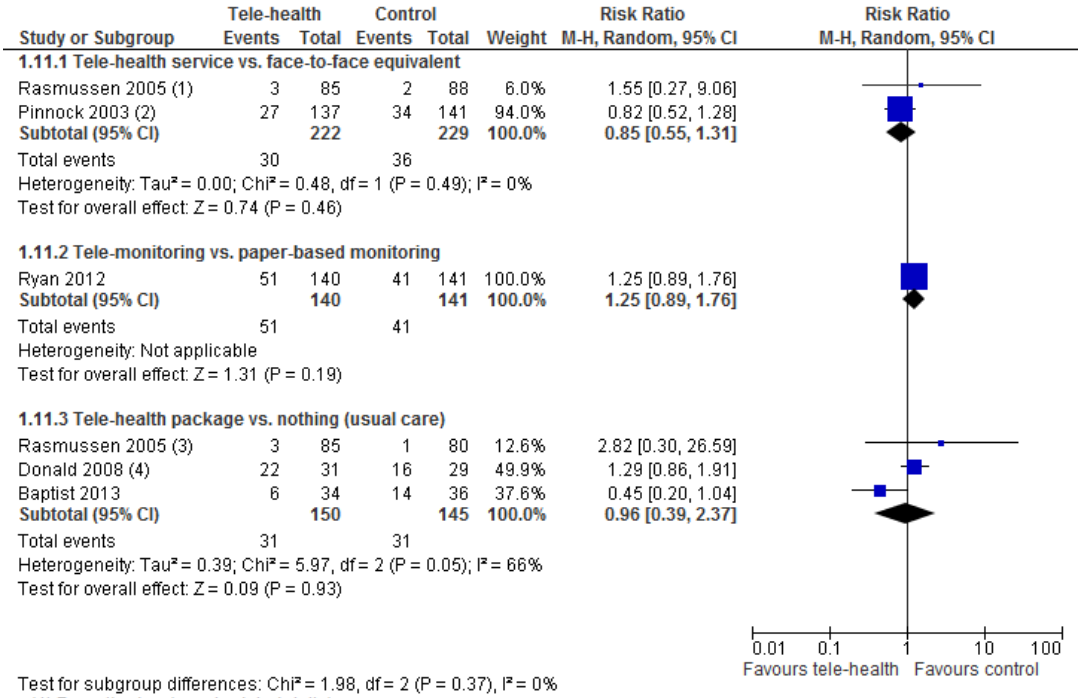


Figure 277: Asthma Control Questionnaire (ACQ)



(1) Random effects used due to heterogeneity in this comparison. Did not affect results for 1.10.1 and 1.10.3.

Figure 278: UHU GP visits



(1) Described as 'unscheduled visits'
(2) Unclear if unscheduled, or total GP visits during the study period
(3) Described as 'unscheduled healthcare visits'
(4) Random effects used due to heterogeneity in this comparison. Point estimates for 1.11.1 and 1.11.2 marginally affected.

Figure 279: Change in forced expiratory volume in 1 second (FEV_1, mL)

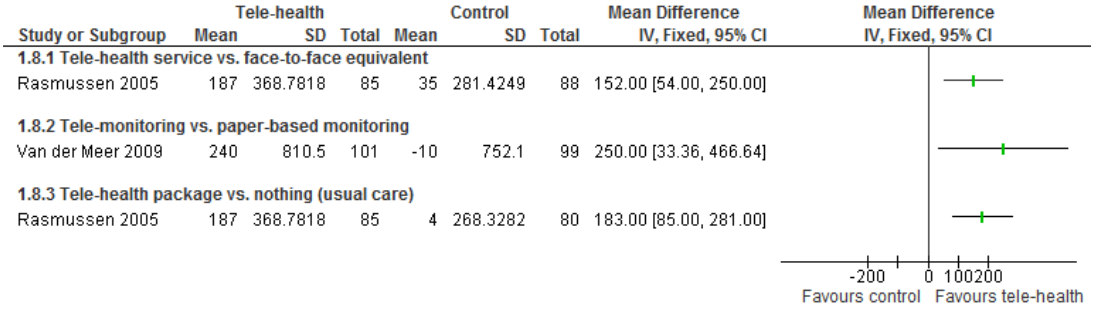


Figure 280: Percentage predicted forced expiratory volume in 1 second (FEV_1)

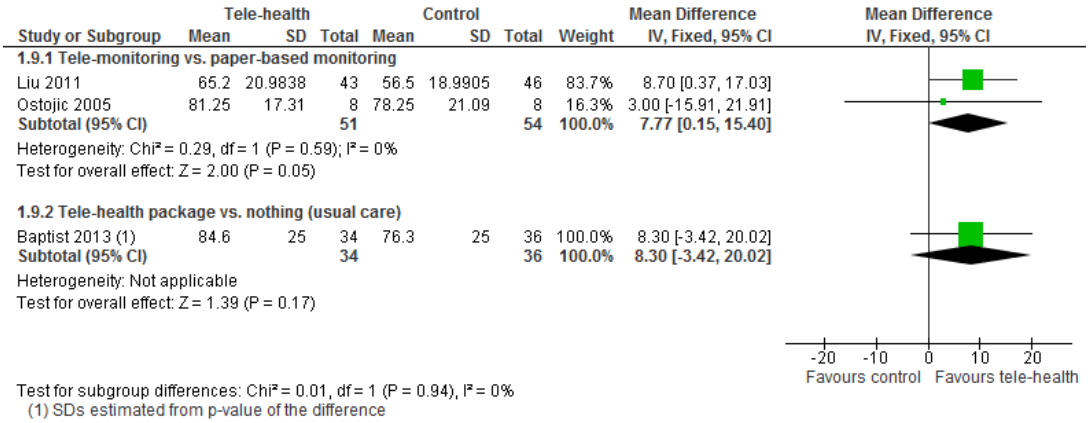


Figure 281: Peak expiratory flow (PEF, litres per minute)

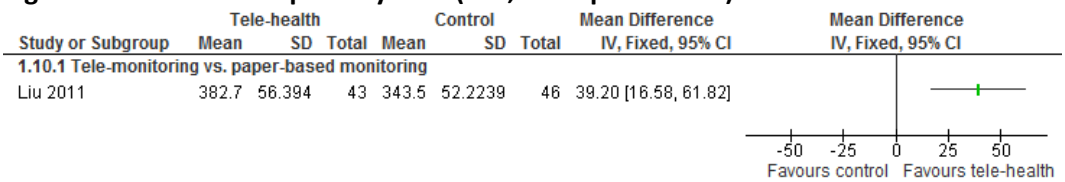
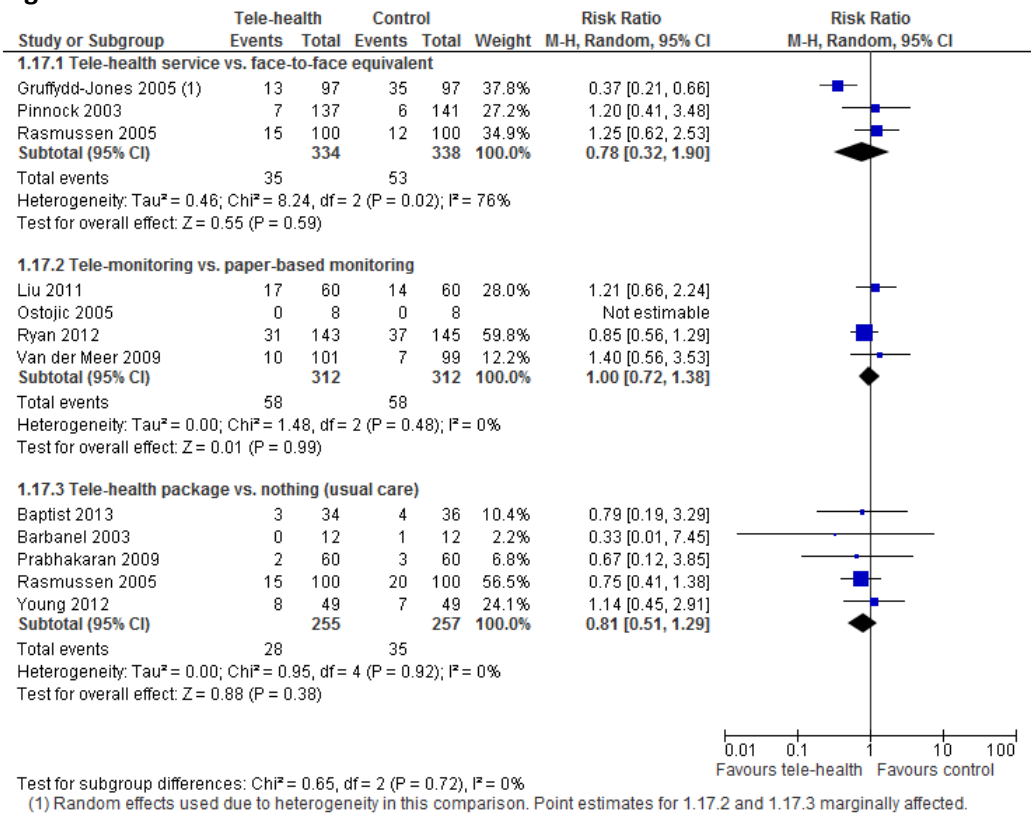


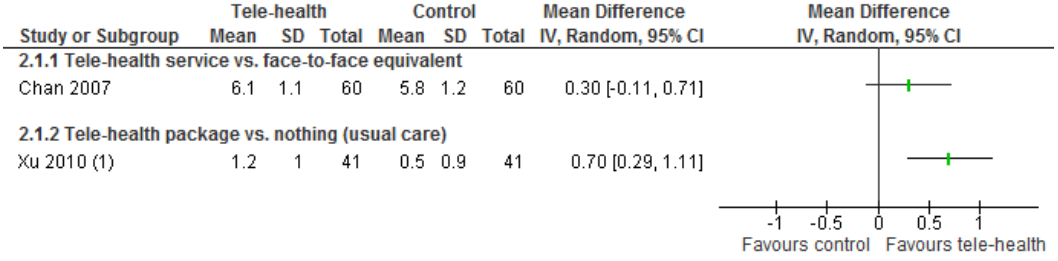
Figure 282: Withdrawal



(1) Random effects used due to heterogeneity in this comparison. Point estimates for 1.17.2 and 1.17.3 marginally affected.

J.21.1.2 Tele-healthcare for children aged 5 to 17

Figure 283: Paediatric Asthma Quality of Life Questionnaire (PAQLQ) – child subscale



(1) change scores

Figure 284: Paediatric Asthma Quality of Life Questionnaire (PAQLQ) – caregiver subscale

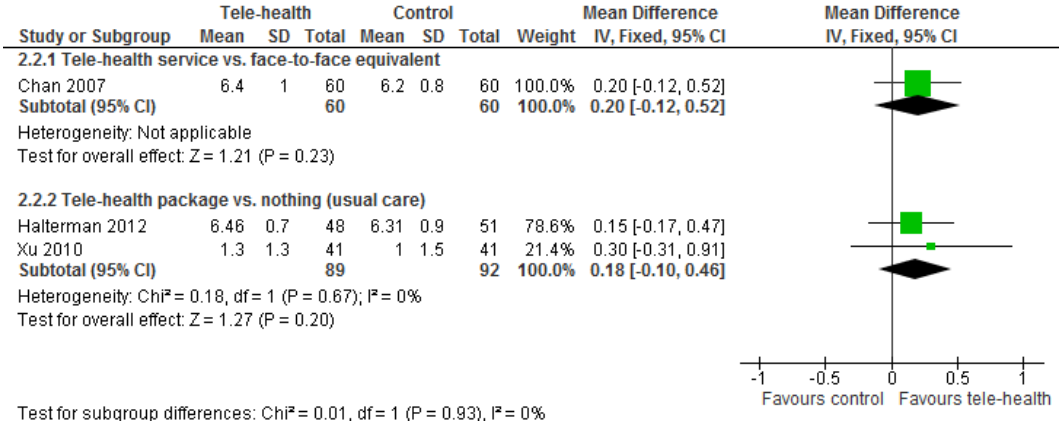


Figure 285: UHU hospitalisation

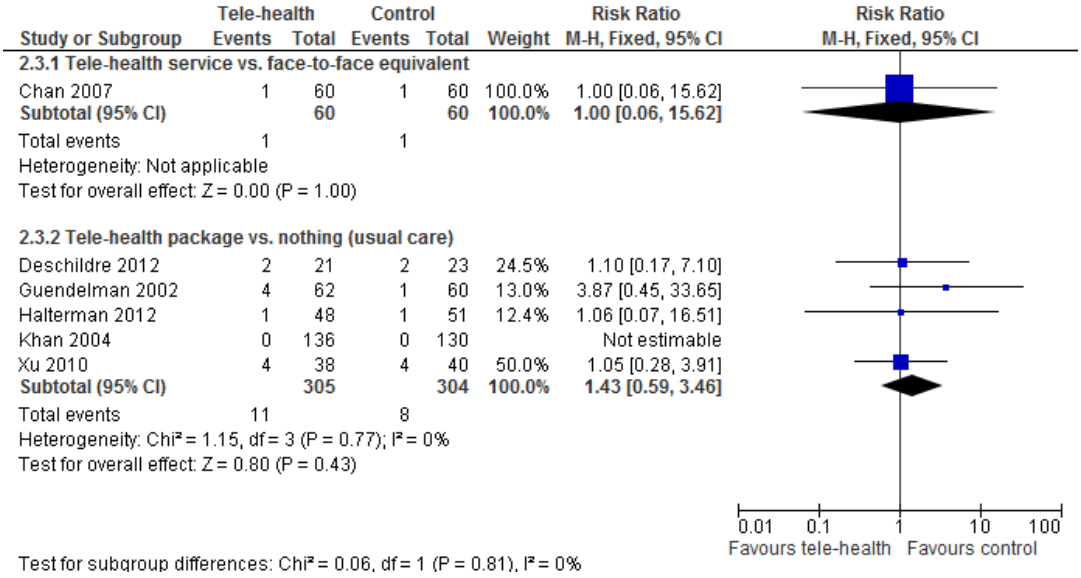


Figure 286: UHU ED visit

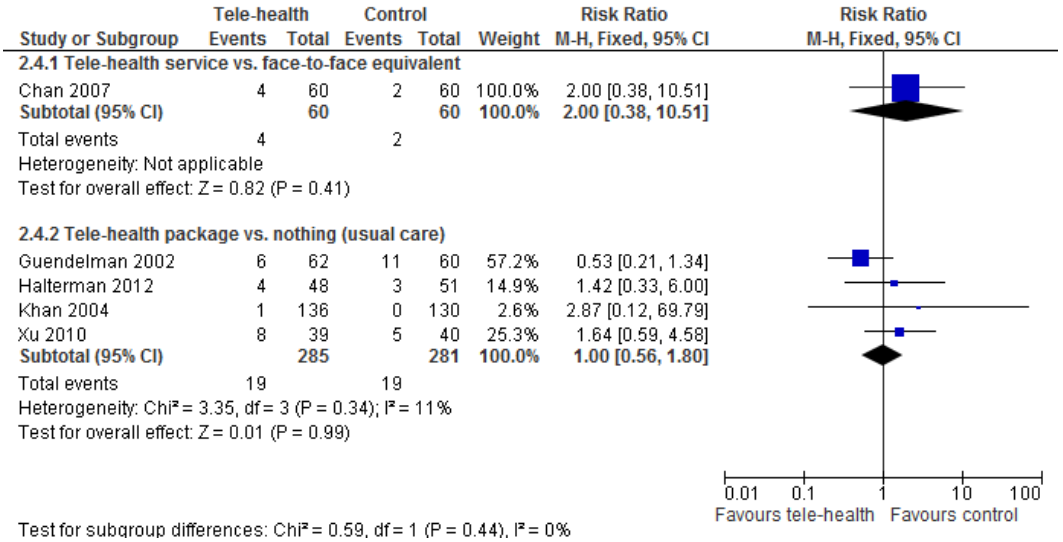


Figure 287: Exacerbations requiring oral steroids

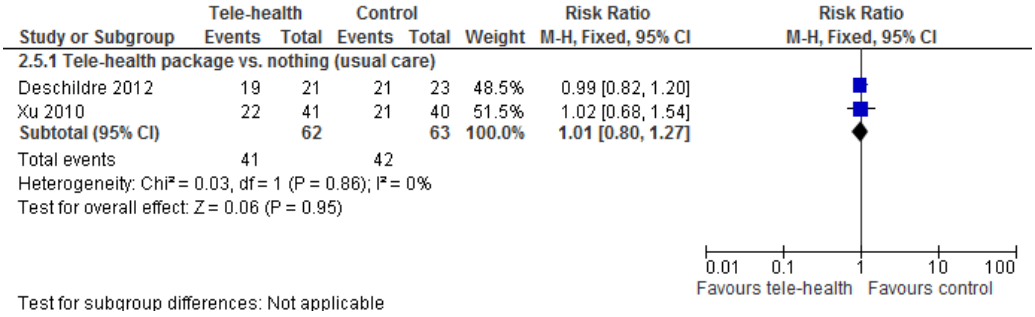


Figure 288: Asthma Control Questionnaire (ACQ)

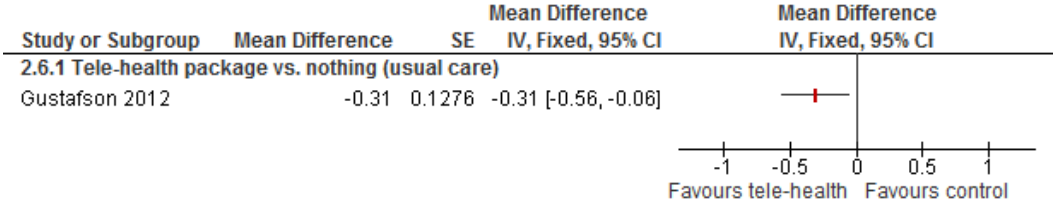


Figure 289: UHU GP visits

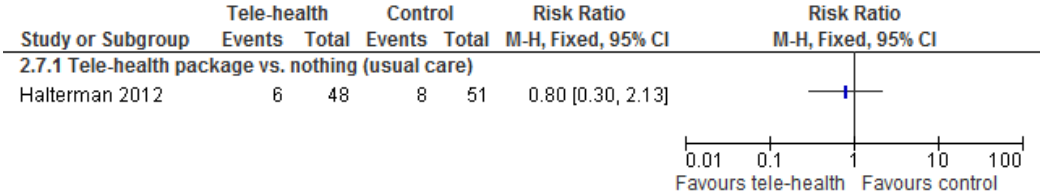


Figure 290: Percentage predicted forced expiratory volume in 1 second (FEV_1)

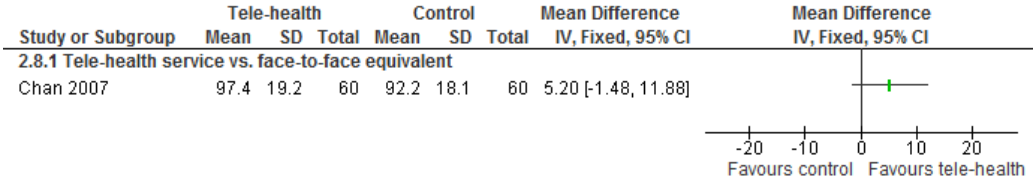


Figure 291: Change in morning peak expiratory flow (PEF, litres per minute)

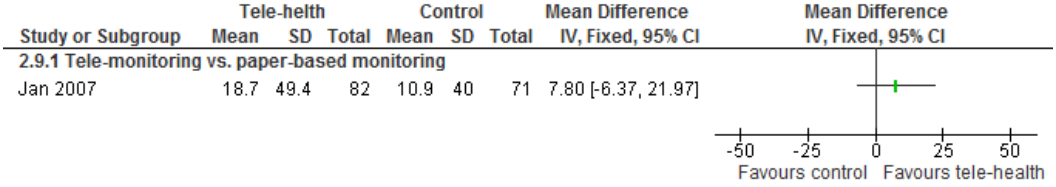


Figure 292: Change in evening peak expiratory flow (PEF, litres per minute)

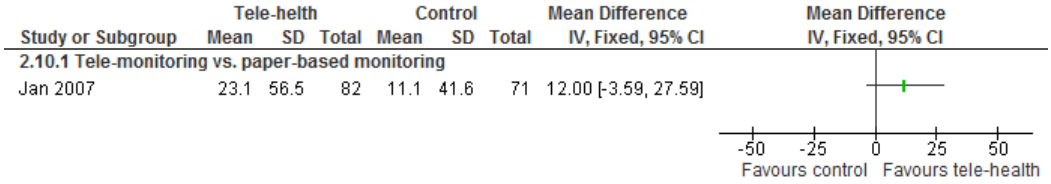
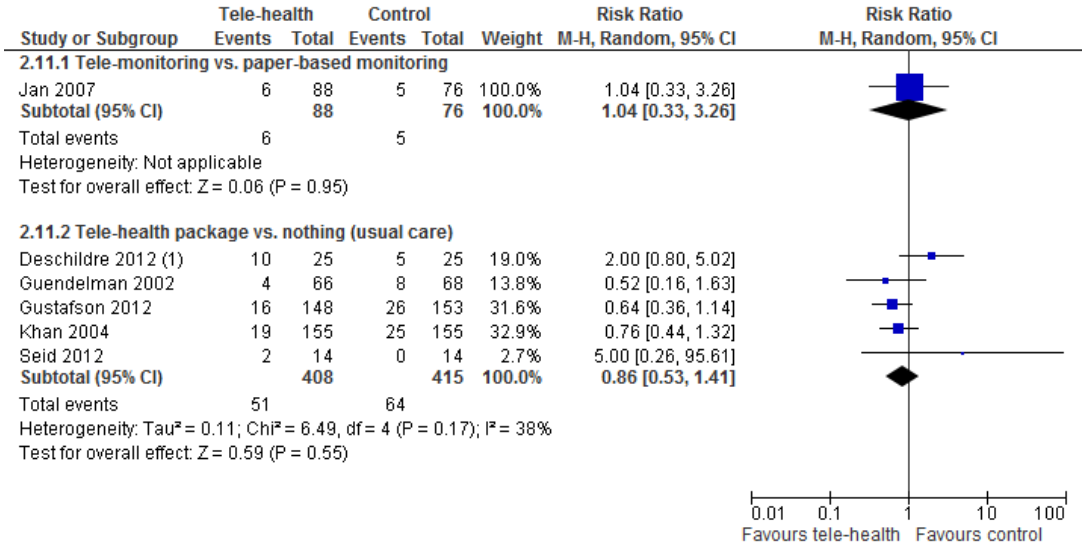


Figure 293: Withdrawal



(1) Random effects used due to heterogeneity in this comparison. Point estimate for 2.11.1 not affected.

J.21.1.3 Adults and young people (>16 years): Telehealthcare without healthcare professional involvement vs usual care

Figure 294: QOL <6 months (AQLQ, range 0-7)

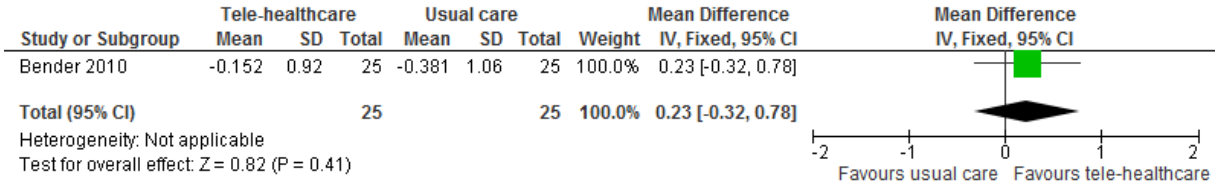
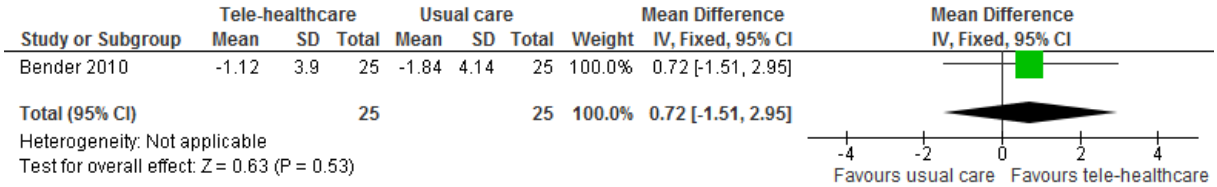


Figure 295: Asthma control questionnaires <6 months (ACT, range 5-25)



J.21.1.4 Children (5-16 years): Telehealthcare without healthcare professional involvement vs usual care

Figure 296: Exacerbations ≥6 months (OCS rescue use)

Figure 297: QOL ≥6 months (pAQLQ carer).

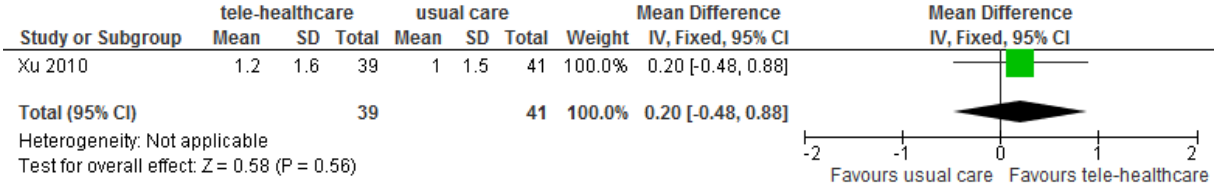


Figure 298: QOL ≥6 months (pAQLQ child).

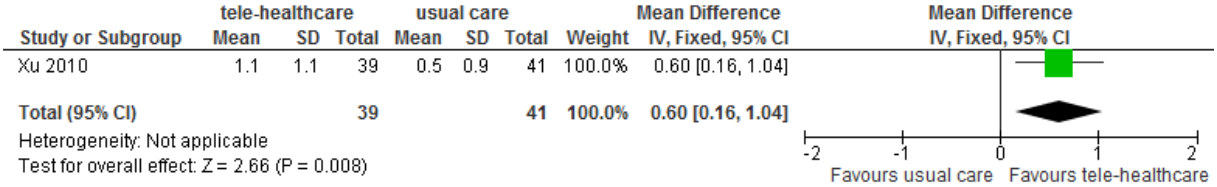


Figure 299: UHU ≥6 months (self-report ED presentation)

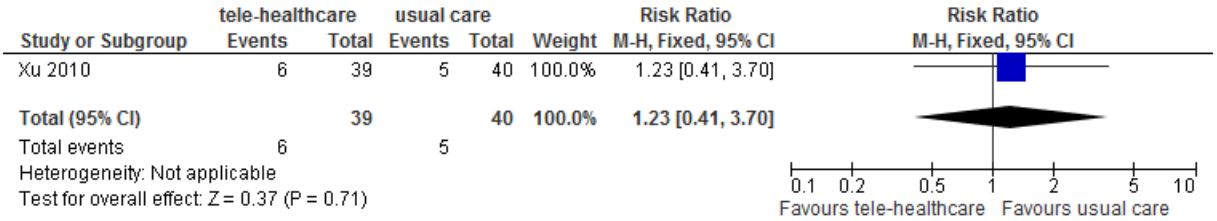


Figure 300: UHU ≥6 months (self-report hospitalisation)

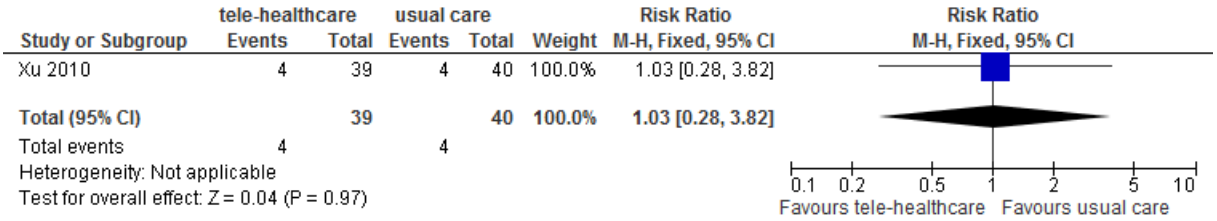


Figure 301: School days lost ≥6 months (self-report yes/no)

Figure 302: Parent work days lost ≥6 months (self-report yes/no)

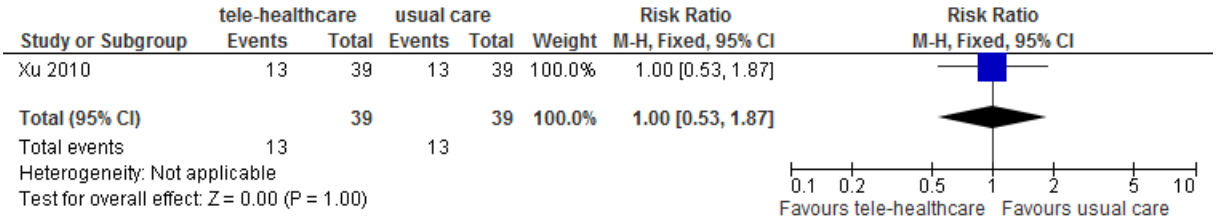


Figure 303: Patients who should have been on controllers at baseline (i.e. persistent asthma) but were not, who were on controllers at 6 months

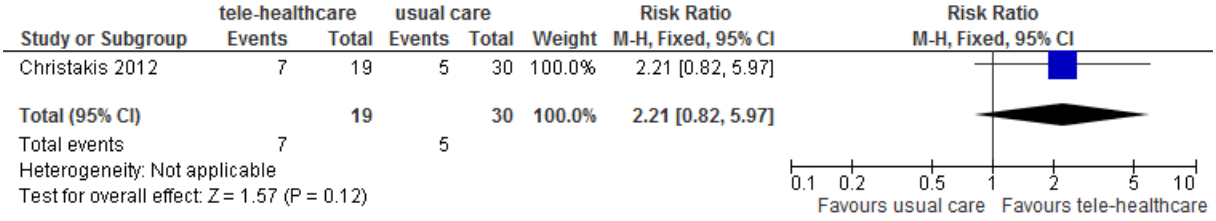


Figure 304: Persistent asthma on controllers at baseline but discontinued at 6 months.

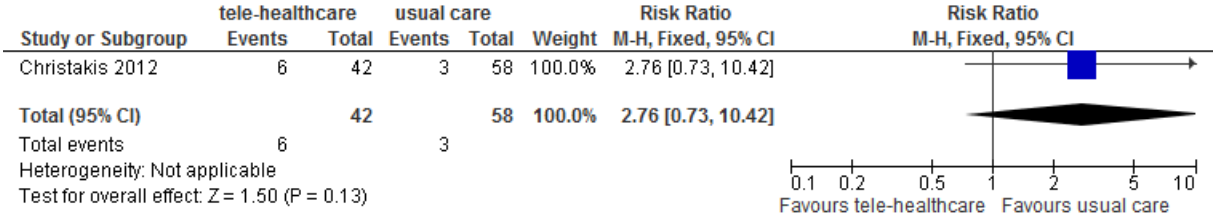
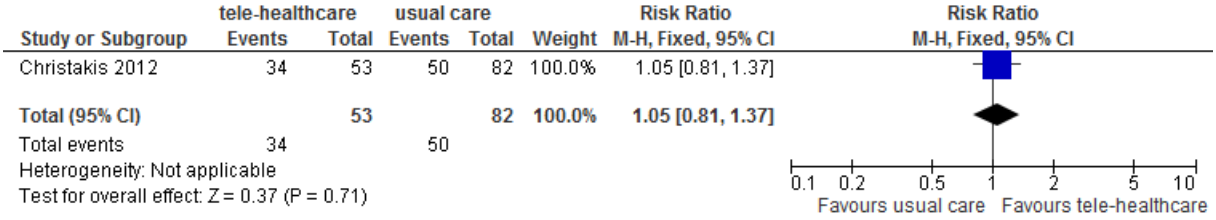


Figure 305: Of those who met severity criteria for controllers at baseline, number on them at 12 months



Appendix K: Excluded clinical studies

K.1 Diagnosis: Signs and symptoms

Table 209: Studies excluded from the clinical review

Reference	Reason for exclusion
ABRAMSON 1992[9]	General population and no subgroup analysis
ABRAMSON 1996A[10]	General population and no subgroup analysis
ABRAMSON 2002[12]	Wrong definition of Phys Dx – no objective test.
AMAT 2011[41]	Wrong definition of Phys Dx – no objective test.
ANDERSON 1986[44]	Wrong definition of Phys Dx – no objective test.
ANDERSON 1987[45]	Wrong definition of Phys Dx – no objective test.
ANTOLINAMERIGO 2012[54]	Conference abstract
ARIF 2003[67]	General population and no subgroup analysis
ARIF 2004[66]	Older children: wrong definition of Phys Dx – no objective test. Younger children: looks at wrong risk factors (not those specified in our protocol).
ARIF 2007[69]	Wrong definition of Phys Dx – no objective test.
ARIF 2008[68]	General population and no subgroup analysis; QoL only given in asthma subgroup.
ARNEDOPENA 2009[73]	General population and no subgroup analysis
ARSHAD 2005[74]	Wrong definition of Phys Dx – no objective test.
ASHER 2008[76]	Wrong definition of Phys Dx – no objective test.
ATHERTON 1996[77]	Wrong definition of Phys Dx – no objective test.
AUSTIN 1997[79]	RFs for wheeze, not asthma.
BACHARIER 2012[86]	Asthma (wheeze in children) and no comparison group.
BACKER 2009[89]	No comparison group – asthma only.
BAI 1998[93]	Wrong definition of Phys Dx – no objective test.
BALL 2000[99]	Gives prevalence of asthma

Reference	Reason for exclusion
	but not symptoms.
BARRY 2012[117]	General population and no subgroup analysis, and looks at the wrong risk factors (not those specified in our protocol),
BAUMAN 1992[128]	Wrong definition of Phys Dx – no objective test.
BAUMANN 1986[129]	Wrong comparison group: asthma vs. healthy controls.
BEACH 1995[134]	Diurnal variation in methacholine results, not in symptoms.
BEEH 2003[137]	Wrong population: only patients without asthma.
BELAMARICH 2000[143]	Wrong definition of Phys Dx – no objective test.
BELLIA 2000[148]	Wrong definition of Phys Dx – no objective test.
BENTUR 2004[154]	Wrong definition of Phys Dx – no objective test.
BERG 2004[158]	General population and no subgroup analysis
BERG 2011[155]	Wrong definition of Phys Dx – no objective test.
BERZ 2007[166]	Correct Phys Dx, but Looks at the wrong risk factors (not those specified in our protocol), and gives prevalence in people with asthma with no comparison group.
BISGAARD 2011[176]	Wrong population for sens/spec: general population. Wrong populatin for prevalence data: asthma or general population, nt asthma vs. other respiratory diseases. Predictors of asthma development are not given in useable categories.
BOLLAG 2000[184]	Wrong outcomes: asthma attack rates.
BONER 2010[187]	Wrong definition of Phys Dx – no objective test.
BORREGO 2009 A [194]	Does not give the % of people with asthma.
BORREGO 2010[195]	Looks at the wrong risk factors (not those specified in

Reference	Reason for exclusion
	our protocol).
BOUDREAU 1995[201]	Wrong results: presence of symptoms during histamine challenge.
BOULET 1991[203]	Asthma pts only and no comparison group.
BOUSQUET 2004[205]	Wrong definition of Phys Dx of asthma only group – no objective test.
BRAUNFAHRLANDER 1998[220]	Wrong definition of Phys Dx – no objective test.
BRAUNFAHRLANDER 2004[221]	General population and no subgroup analysis
BRENNER 2001[223]	Wrong definition of Phys Dx – no objective test.
BRESCIANINI 2009[224]	Wrong definition of Phys Dx – no objective test.
BROEKHUIZEN 2010[228]	Cannot calculate sensitivity and specificity
BROOKE 1998[230]	Wrong definition of Phys Dx – no objective test.
BRUTSCHE 2006[239]	Wrong outcomes/population: prevalence of symptoms in previously asymptomatic pts.
BURNEY 1989[248]	Wrong outcomes: sens/spec for wheeze, asthma attack, or bronchial irritability, not asthma Dx.
BURROWS 1991[250]	Wrong definition of Phys Dx – no objective test.
BUSINCO 1979[253]	Gives prevalence of people with asthma (wheezers) only, no comparison group.
CAREY 1996[272]	Wrong definition of Phys Dx – no objective test.
CARTER 2006[286]	Wrong definition of Phys Dx – no objective test.
CAUDRI 2007[292]	Wrong definition of Phys Dx – no objective test.
CAUDRI 2009[293]	Wrong definition of Phys Dx – no objective test.
CAUDRI 2010[294]	Wrong outcomes: risk factors for future asthma symptoms not asthma Dx. Prevalence of symptoms in suspected asthma but not in asthma vs. other respiratory diseases.
CHANG 2013[299]	Population does not match

Reference	Reason for exclusion
	protocol – family history of respiratory allergy
CHINN 2004[313]	General population and no subgroup analysis
CHRISTOFF 2013[323]	Conference abstract
COLEMAN 2001[355]	Wrong definition of Phys Dx – no objective test.
CORDEIRO 2011[360]	Population does not match protocol – general allergic symptoms not respiratory symptoms only.
CORTESALVAREZ 2007[363]	Reference standard does not match protocol – history of atopic disorders in ≤ 3 yrs with wheezing, but no Dx of asthma made
COURT 2002[367]	Wrong definition of Phys Dx – no objective test.
CSONKA 2000A[377]	Wrong definition of Phys Dx – no objective test.
CUIJPERS 1994[378]	Wrong definition of Phys Dx – no objective test.
DALES 1987[386]	Wrong outcomes: sens/spec and predictors of AHR not asthma.
DALES 1988[387]	Wrong outcomes: predictors of AHR not asthma.
DAS 2003[388]	Levels of IgE in wheezers v. controls. Not signs and symptoms.
DEBENEDICTIS 1986[391]	Not known who had asthma, but only people with chronic cough who were MCT positive.
DEMARCO 2005[399]	Wrong definition of Phys Dx – no objective test.
DEMARCO 2006[400]	Prognostic factors for asthma severity, rather than for developing asthma.
DEN OTTER 1998[418]	Wrong outcomes; symptoms in people who consulted the GP vs. those who did not, rather than people with asthma.
DODGE 1994[440]	Wrong definition of Phys Dx – no objective test.
DODGE 1996[441]	Wrong definition of Phys Dx – no objective test.

Reference	Reason for exclusion
FANIRAN 1999[485]	General population and no subgroup analysis
FLEMING 2000[499]	Prevalence of asthma over time rather than symptoms.
FOUCARD 1984[507]	Reference standard does not match protocol (children who reported asthma symptoms during the last year were regarded as having asthma)
FRANK 1996[510]	Wrong definition of Phys Dx – no objective test.
FRANK 2001[511]	Wrong definition of Phys Dx – no objective test.
FRANK 2008[512]	Predictors of wheeze, not asthma.
FRISCHER 1993[518]	Wrong definition of Phys Dx – no objective test.
FUJIMURA 2005[527]	Looks at the wrong risk factors (not those specified in our protocol).
GARCINUNO 2013[544]	Wrong definition of Phys Dx – no objective test.
GERALD 2009[550]	Cannot calculate sensitivity and specificity
GLASGOW 2001[568]	General population and no subgroup analysis; and sens/spec not in suspected asthma.
GODDEN 1994[569]	Meets all inclusion criteria for prevalence study, except wrong sample size, N<200.
GOKSOR 2006[576]	Wrong definition of Phys Dx – no objective test.
GOKSOR 2008[577]	Wrong definition of Phys Dx – no objective test.
GUERRA 2004[605]	Wrong definition of Phys Dx – no objective test.
GUILBERT 2004A[607]	Wrong definition of Phys Dx – no objective test.
GUILBERT 2004B[606]	Risk factors for wheeze in adults, not asthma.
GUILBERT 2011A [608]	Wrong definition of Phys Dx – no objective test.
HABBICK 1999[613]	Wrong definition of Phys Dx – no objective test.
HABY 2001[614]	Looks at the wrong risk

Reference	Reason for exclusion
	factors (not those specified in our protocol). Prevalence in general population.
HAFKAMP 2012[618]	Looks at the wrong risk factors (not those specified in our protocol).
HAFKAMP 2013[617]	Wrong definition of Phys Dx – no objective test.
HAFKAMP 2013A [616]	Prevalence in general population.
HAHN 1994[619]	Wrong definition of Phys Dx – no objective test.
HALL 2006[621]	Wrong definition of Phys Dx – no objective test.
HALLIDAY 1993[623]	Wrong definition of Phys Dx – no objective test.
HALONEN 1999[624]	Looks at the wrong risk factors (not those specified in our protocol). Prevalence in general population.
HALONEN 2013[625]	Looks at the wrong risk factors (not those specified in our protocol). Prevalence in general population.
HANCOX 2004[628]	Wrong definition of Phys Dx – no objective test.
HANCOX 2005[629]	Looks at the wrong risk factors (not those specified in our protocol).
HANCOX 2006[630]	Wrong definition of Phys Dx – no objective test.
HANSEL 2011[632]	Cannot calculate sensitivity and specificity
HEINRICH 1998[652]	Prevalence in general population.
HEINRICH 1999[651]	Prevalence in general population. Looks at the wrong risk factors (not those specified in our protocol).
HEINRICH 2002[650]	Wrong definition of Phys Dx – no objective test.
HENDERSON 1995[655]	Predictor of wheeze, not asthma.
HENDERSON 2005[657]	Prevalence in wrong population: RSV pts vs. controls, not asthma vs. other respiratory diseases.

Reference	Reason for exclusion
HENDERSON 2008[656]	Wrong definition of Phys Dx – no objective test.
HENDERSON 2008A[658]	Wrong definition of Phys Dx – no objective test.
HENSLEY 2003[662]	Prevalence in wrong population: not asthma vs. other respiratory diseases.
HERR 2012[664]	Age 18 months, but assessment of symptoms made in the previous 12 months.
HERR 2012A[663]	Age 18 months, but assessment of symptoms made in the previous 12 months.
HICKSON 2009[668]	Prevalence in general population.
HIRSCH 1999[674]	Wrong definition of Phys Dx – no objective test.
HIRSCH 2004[673]	Looks at a new score for Dx of asthma. However the score contains other aspects as well as symptoms, and results are not given separately for the symptoms.
HODGE 1996[675]	Looks at the wrong risk factors (not those specified in our protocol).
HOEK 2012[676]	Prevalence in general population.
HOLSTER 2012[682]	Wrong definition of Phys Dx – no objective test. Looks at the wrong risk factors (not those specified in our protocol).
HOLT 2010[684]	Prevalence in general population. Looks at the wrong risk factors (not those specified in our protocol).
HOMNICK 2007[688]	Wrong definition of Phys Dx – no objective test.
HOPP 1995[694]	Dx ability of questionnaire but looks at asthma a vs. controls in general population, not suspected asthma pts.
HOPPER 1995[695]	Prevalence in general population.
HOPPER 2012[696]	Wrong definition of Phys Dx – no objective test.

Reference	Reason for exclusion
HORAK 2003[697]	Wrong definition of Phys Dx – no objective test.
HORAK 2006[699]	Prevalence in general population.
HORAK 2007[698]	Prevalence in general population. Looks at the wrong risk factors (not those specified in our protocol).
HORWOOD 1985[702]	Meets all inclusion criteria for prognostic study in children, except wrong follow-up time: 6 years.
HU 1997[707]	Prevalence in general population. Looks at the wrong risk factors (not those specified in our protocol).
HU 1997A[706]	Wrong definition of Phys Dx – no objective test.
HUBLET 2006[710]	Prevalence in general population.
HUNGER 2010[712]	Wrong definition of Phys Dx – no objective test.
ILLI 2001[725]	Wrong definition of Phys Dx – no objective test.
ILLI 2001A[724]	Prevalence in general population.
ILLI 2004[726]	Wrong definition of Phys Dx – no objective test.
ILLI 2006[727]	Wrong definition of Phys Dx – no objective test.
INKLEY 1967[730]	Prevalence in general population.
IRWIN 1990[731]	Gives the prevalence of asthma in people with cough, not the prevalence of cough in people who do not have asthma.
ISLAM 2007[734]	Wrong definition of Phys Dx – no objective test.
IVERSEN 2005[735]	Wrong definition of Phys Dx – no objective test.
JACKSON 2008[739]	Wrong definition of Phys Dx – no objective test.
JACOBS 2012[740]	Wrong definition of Phys Dx – no objective test.
JAMES 2010[745]	Wrong definition of Phys Dx – no objective test.

Reference	Reason for exclusion
JAMES 2013[746]	Prevalence in general population.
JAMROZIK 2009[748]	Wrong definition of Phys Dx – no objective test.
JANSON 2001[752]	Wrong definition of Phys Dx – no objective test.
JANSON 2001A [753]	Wrong definition of Phys Dx – no objective test.
JARTTI 2008[758]	Wrong definition of Phys Dx – no objective test.
JARVIS 1994[761]	Prevalence in general population.
JARVIS 1996[759]	Wrong definition of Phys Dx – no objective test.
JARVIS 2002[760]	Wrong definition of Phys Dx – no objective test.
JEFFS 2000[763]	Unclear Phsy Dx – but seems like ISAAC questionnaire.
JENKINS 1994A[766]	Wrong definition of Phys Dx – no objective test.
JENKINS 2006[765]	Wrong definition of Phys Dx – no objective test.
JOHNSON 2013[772]	General population and no subgroup analysis
JOHNSTON 1998[773]	Risk factors for other respiratory problems, not asthma. Prevalence of people with asthma with no comparison group.
JONES 2008[777]	Results separated for different ethnic groups. Mixed ages of children (<5 and >5 years with no subgroup analysis). Wrong definition of Phys Dx – no objective test.
JOSEPH 1996[780]	Wrong definition of Phys Dx – no objective test.
JOSEPH 1999[781]	Reference standard does not match protocol (self-reported physician Dx of asthma – no objective test).
JOSEPH-BOWEN 2004[783]	Reference standard does not match protocol; physician diagnosis + symptoms of wheeze in last 12 months + asthma meds in last 12 months (no objective test)
JUHN 2005[784]	Looks at the wrong risk

Reference	Reason for exclusion
	factors (not those specified in our protocol). Unclear percentage who had objective test with the Phys Dx.
JUNG 2012[787]	Looks at the wrong risk factors (not those specified in our protocol). Prevalence in general population.
JUNG 2012A[786]	Predictors of wheeze, not asthma.
JUST 2010[801]	Predictors of wheeze, not asthma.
JUST 2013[802]	Wrong outcome: predictors of different types of wheeze.
KABESCH 2004[803]	Looks at the wrong risk factors (not those specified in our protocol). Prevalence in general population.
KABIR 2009[804]	Wrong definition of Phys Dx – no objective test.
KABLE 2001[805]	Prevalence and sens/spec in general population.
KAGEN 2014[806]	Conference abstract
KAPPELLE 2012[812]	Wrong definition of Phys Dx – no objective test.
KARAKOC 2002[817]	Prevalence in general population, and looks at wrong risk factors (not those specified in our protocol).
KAUFFMANN 1997[822]	Wrong definition of Phys Dx – no objective test.
KAUFFMANN 2011[823]	Epidemiology.
KAUGARS 2008[825]	Looks at wrong risk factors (not those specified in our protocol).
KEALL 2012[829]	Prevalence in general population.
KEARNEY 1998[830]	Wrong definition of Phys Dx – no objective test.
KEIL 1996[833]	General population and no subgroup analysis
KEIL 2006[832]	Review – used as a source of references
KELLY 1987[834]	Unclear Phys Dx. Case-control study.
KELLY 1995[835]	Wrong definition of Phys Dx –

Reference	Reason for exclusion
	no objective test.
KELLY 1996[836]	Wrong definition of Phys Dx – no objective test.
KERCSMAR 2008[841]	Conference summary.
KERKHOF 2009[843]	Wrong definition of Phys Dx – no objective test.
KHARITONOV 1996[851]	Asthma only – no comparison group. Correct Phys Dx with objective test.
KHOSHOO 2009[854]	Meets all inclusion criteria for prevalence study, except sample size N<200.
KIEFTEDE 2012[855]	Looks at wrong risk factors. Prevalence in general population.
KING 2004[867]	Predictors of lung function, not asthma. Does not give prevalence in asthma pts.
KISS 2003[868]	Symptoms as predictors of angina, not asthma! Unclear asthma Dx.
KLAASSEN 2012[874]	Does not give prevalence of symptoms, or predictors, or ability to diagnose.
KLINNERT 2001[879]	Wrong definition of Phys Dx – no objective test.
KLINNERT 2008[880]	General population and no subgroup analysis, and looks at wrong risk factors (not those specified in out protocol).
KLJAKOVIC 1991[881]	General population and no subgroup analysis
KNEYBER 2000[882]	Does not give symptoms in asthma, but bronchiolitis and control group.
KOLLER 1997[893]	Age < 1 year
KOLNAAR 1995[894]	Reference standard does not match protocol - comparison of histamine test to presence of asthma symptoms (not to physician Dx)
KOPONEN 2012[901]	Wrong definition of Phys Dx – no objective test.
KOSHY 2010[903]	General population and no subgroup analysis
KOZYRSKYJ 2003[916]	Wrong definition of Phys Dx –

Reference	Reason for exclusion
	no details given or mention of objective test.
KOZYRSKYJ 2004[917]	Wrong definition of Phys Dx – no objective test.
KOZYRSKYJ 2009[915]	Wrong definition of Phys Dx – no objective test.
KUEHNI 2000[921]	Wrong definition of Phys Dx – no objective test.
KUEHNI 2001[922]	Prevalence of symptoms in people with asthma only, no comparison group.
KUEHR 1995[924]	Wrong comparison group: asthma vs. non-asthma (not other respiratory symptoms).
KUHNI 1995[926]	Does not mention asthma definition of Dx.
KUMAR 2008[930]	General population and no subgroup analysis
KURUKULAARATCHY 2002[935]	Gives prevalence data in people with asthma but no other respiratory comparison group. Prognostic data not used as wrong follow-up time: baseline (birth) to 10 years later (does not match our protocol criteria).
KURUKULAARATCHY 2003[937]	Risk of wheeze not asthma (older children).
KURUKULAARATCHY 2003A[939]	Asthma only - no comparison group.
KURUKULAARATCHY 2004[934]	Wrong population: wheeze not asthma (older children).
KURUKULAARATCHY 2004A[938]	General population and no subgroup analysis
KURUKULAARATCHY 2005[940]	General population and no subgroup analysis; looks at wrong risk factors (not those in our protocol).
KURUKULAARATCHY 2005A[936]	Prevalence and risk factors for atopy, not asthma.
LABRUZZO 2007[945]	Review.
LAI 2009[949]	General population and no subgroup analysis
LANGE 2010[953]	General population and no subgroup analysis
LAU 2000[961]	General population and no subgroup analysis

Reference	Reason for exclusion
LAU 2002[963]	Prevalence in wheezers (young children) but no comparison group.
LAU 2003[962]	Predictors of impaired lung function not asthma.
LAU 2005[960]	Wrong definition of Phys Dx – no objective test.
LAUBEREAU 2002[964]	General population and no subgroup analysis
LEERMAKERS 2013[974]	General population and no subgroup analysis
LEONARDI 2011[982]	Wrong definition of Phys Dx – no objective test.
LEONE 2012[983]	Wrong definition of Phys Dx – no objective test.
LESOUEF 1995[969]	General population and no subgroup analysis
LEUNG 1994[986]	Wrong definition of Phys Dx – no objective test.
LEVESQUE 2004[989]	Wrong definition of Phys Dx – no objective test.
LEWIS 1995[993]	Predictors of wheeze not asthma (in young people).
LEWIS 1996[992]	General population and no subgroup analysis
LI 2006B[998]	Wrong definition of Phys Dx – no objective test.
LIEM 2007[1001]	RFs for transient tachypnea and wheeze, not asthma.
LINEHAN 2007[1010]	General population and no subgroup analysis.
LINEHAN 2009[1009]	Prevalence in people with respiratory symptoms, not asthma.
LINEHAN 2012[1008]	General population and no subgroup analysis.
LOERBROKS 2012[1024]	Prevalence in general population but not in asthma subgroup.
LUYT 1993[1041]	General population or asthma subgroup (no comparison group).
LUYT 1994[1040]	Wrong definition of Phys Dx for children up to 5 years old: no objective test, just symptoms ascertained by

Reference	Reason for exclusion
	questionnaire.
LUYT 1995[1039]	General population or asthma subgroup (no comparison group). Looks at wrong risk factors (not those specified in our protocol).
MAAS 2009[1042]	Does not answerthe question. Effect of allergen-reduction interventions on the prevention of asthma.
MAGDALIJNS 2011[1047]	General population and no subgroup analysis
MAHER 2004[1051]	Cannot calculate sensitivity and specificity
MAITRA 2004[1054]	General population and no subgroup analysis
MALLOL 2010[1062]	Percentage of wheezers who had asthma, rather than % of asthma who had wheeze.
MANDHANE 2005[1070]	RFs for wheeze, not asthma.
MANFREDA 2001[1071]	Wrong definition of Phys Dx – no objective test.
MANNING 2007[1072]	Conference abstract.
MARBURY 1996[1076]	General population and no subgroup analysis
MAROSSY 2007[1079]	Wrong definition of Phys Dx – no objective test.
MARTINDALE 2005[1080]	General population and no subgroup analysis
MARTINEZ 1995[1081]	General population and no subgroup analysis
MARTINEZ 2006[1082]	General population and no subgroup analysis
MATHESON 2006[1087]	Looks at the wrong risk factors (not those specified in our protocol).
MATRICARDI 2008[1089]	Predictors of wheeze not asthma (in young people).
MAZIAK 2002[1097]	Wrong definition of Phys Dx – no objective test.
MAZIAK 2004[1098]	Wrong definition of Phys Dx – no objective test.
MCCONNELL 1999[1101]	Wrong definition of Phys Dx – no objective test.
MCCONNELL 2002[1102]	Wrong definition of Phys Dx –

Reference	Reason for exclusion
	no objective test.
MCHEDLISHVILI 2013[1108]	Conference abstract
MCKEEVER 2002[1109]	Unclear age of children and follow-up time.
MICHEL 2006[1129]	Dx of wheeze in older children (not asthma).
MIDODZI 2010[1131]	Wrong definition of Phys Dx for children up to 5 years old: no objective test, just symptoms ascertained by questionnaire.
MIEDINGER 2007[1134]	Good definition of Phys Dx, but gives sens/spec in general population (not suspected asthma), and prevalence in asthma pts only (no comparison group).
MILAM 2008[1136]	No comparison group: wheeze only.
MILLSTEIN 2004[1142]	Wrong definition of Phys Dx – no objective test. Wrong definition of Phys Dx – no objective test.
MITCHELL 1989[1150]	General population and no subgroup analysis.
MITCHELL 1994[1148]	Wrong definition of Phys Dx – no objective test.
MITCHELL 1997[1152]	Methods paper – not study results.
MITCHELL 2009[1151]	Predictors of wheeze, not asthma (older children)
MOHANGOO 2010[1159]	Good definition of Phys Dx, but gives sensitivity/specificity in general population (not suspected asthma), and prevalence in general population (not people with asthma).
MOMAS 1998[1160]	Wrong definition of Phys Dx – no objective test.
MOMMERS 2005[1161]	Wrong comparison group - - prevalence in asthma vs. controls (not vs. other respiratory diseases), and looks at the wrong risk factors (not those specified in our protocol).
MORASS 2008[1166]	General population and no

Reference	Reason for exclusion
	subgroup analysis; looks at the wrong risk factors (not those specified in our protocol).
MORGAN 2005[1167]	Literature review.
MUSK 2011[1185]	Wrong definition of Phys Dx – no objective test.
MVULA 2005[1189]	General population and no subgroup analysis
NAGEL 2009A[1193]	Looks at the wrong risk factors (not those specified in our protocol).
NAGEL 2010[1195]	Looks at the wrong risk factors (not those specified in our protocol). Prevalence of asthma in general population
NAGEL 2012[1194]	Wrong definition of Phys Dx – no objective test.
NANKANI 1990[1196]	Wrong definition of Phys Dx – no objective test.
NEJJARI 1994[1208]	Case-control study: asthma vs. healthy controls (not other respiratory diseases).
NEUMAN 2012[1210]	Wrong definition of Phys Dx – no objective test.
NEVILLE 1992[1212]	Wrong definition of Phys Dx – no objective test.
NEVILLE 2001[1213]	Prevalence in asthma pts only (no comparison group).
NGMANKWONG 2001[1215]	General population and no subgroup analysis
NGMANKWONG 2002[1214]	Wrong definition of Phys Dx – no objective test.
NICOLAI 2003[1222]	General population and no subgroup analysis
NINAN 1993[1236]	Prevalence data only given in the symptomatic group who are BHR+ (ie people with asthma), not in any comparison group.
NINAN 1995[1235]	Reference standard does not match protocol – Dx made on the basis of symptoms
NWARU 2013[1251]	General population and no subgroup analysis; wrong risk factors (not those specified in the protocol).

Reference	Reason for exclusion
OBERLE 2003[1254]	Wrong definition of Phys Dx – no objective test.
ODDY 1999[1257]	Wrong definition of Phys Dx – no objective test.
ODDY 2000[1255]	Wrong definition of Phys Dx – no objective test.
ODDY 2002[1256]	Wrong definition of Phys Dx – no objective test.
ODDY 2002A[1258]	General population and no subgroup analysis
ODDY 2004[1259]	Wrong definition of Phys Dx – no objective test.
OSMAN 2007[1275]	Wrong definition of Phys Dx – no objective test.
PALMER 2004[1286]	Wrong definition of Phys Dx – no objective test.
PANICO 2007[1289]	General population and no subgroup analysis
PARARAJASINGAM 1992[1295]	General population and no subgroup analysis
PARK 1986[1298]	Wrong definition of Phys Dx – no objective test.
PATERSON 1997[1305]	General population and no subgroup analysis
PATTEMORE 1990[1307]	Reference standard does not match protocol (asthma diagnosis by previous report of a diagnosis but no objective test)
PEARLMAN 2005[1309]	Wrong comparison group: people with asthma on Tx vs. Tx-naiive people with asthma.
PEAT 1991A[1310]	Predictors of wheeze, not asthma (older children).
PEAT 1993[1312]	Good Phys Dx definition, but looks at wrong risk factors for asthma (not in our protocol).
PEAT 1994[1313]	Good Phys Dx definition, but only gives prevalence in General population and no subgroup analysis.
PERSKY 1998[1326]	Asthma and no comparison group.
PERZANOWSKI 2008A[1328]	General population and no subgroup analysis
PETERS 1999[1333]	Wrong definition of Phys Dx – no objective test.

Reference	Reason for exclusion
PINTO 2010[1352]	General population and no subgroup analysis
PIZZICHINI 2000[1353]	Wrong definition of Phys Dx – no objective test.
PLESSMULLOLI 2000[1357]	General population and no subgroup analysis
PLESSMULLOLI 2001[1358]	General population and no subgroup analysis
PONSONBY 2000[1362]	General population - gives prevalence of symptoms in asthma vs. no asthma (not other respiratory diseases).
PONSONBY 2004[1364]	General population and no subgroup analysis
PONSONBY 2008[1365]	General population and no subgroup analysis
POWELL 1995[1372]	Wrong definition of Phys Dx – no objective test.
POWELL 1996[1373]	Wrong definition of Phys Dx – no objective test.
POWELL 1999[1371]	General population and no subgroup analysis
POWER 1995[1376]	Wrong definition of Phys Dx – no objective test.
PRABHU 2010[1379]	Prevalence in general population and asthma, but no comparison group.
PUJADESRODRIGUEZ 2009[1398]	General population and no subgroup analysis
PUJADESRODRIGUEZ 2009A[1399]	Wrong definition of Phys Dx – no objective test.
RADON 2002[1406]	Wrong definition of Phys Dx – no objective test.
RAHERISON 2006[1409]	Prevalence in asthma, but no comparison group.
RASMUSSEN 2002[1420]	Wrong definition of Phys Dx – no objective test.
RAZA 2012[1423]	Wrong definition of Phys Dx – no objective test.
REDLINE 2003[1427]	Cannot calculate sensitivity and specificity
REGNIER 2013[1429]	Looks at the wrong risk factors (not those specified in our protocol).
REMES 2001[1432]	General population and no subgroup analysis; and looks

Reference	Reason for exclusion
	at the wrong risk factors (not those specified in our protocol).
RENNIE 2004[1434]	Prevalence in asthma subgroup, but no comparison group.
RIETVELD 1996[1445]	Wrong population for Dx accuracy – asthma vs. controls rather than suspected asthma.
RIETVELD 1998[1446]	Wrong definition of Phys Dx – no objective test.
RIZWAN 2004[1450]	General population and no subgroup analysis
ROBINSON 2012A[1452]	Correct definition of Phys Dx, but looks at the wrong risk factors (not those specified in our protocol).
RODRIGO 2013[1454]	Treatment study
RODUIT 2009[1456]	General population and no subgroup analysis
RONA 1995[1461]	General population and no subgroup analysis
ROORDA 2001[1462]	Prevalence of symptoms in suspected asthma, but not asthma vs. other respiratory diseases.
ROSIER 1994[1468]	Does not answer the question. Gives data on prevalence of symptoms in patients with asthma vs. patients without asthma. Divides data into severity categories and measurs of function within each category.
SALAM 2004[1486]	Looks at the wrong risk factors (not those specified in our protocol).
SALOME 1987[1488]	Wrong definition of Phys Dx – no objective test.
SAVENIJE 2011[1503]	Wrong definition of Phys Dx – no objective test.
SCARLETT 1995[1504]	General population and no subgroup analysis
SCHACHTER 2001[1507]	Looks at the wrong risk factors (not those specified in our protocol).
SCHACHTER 2003[1506]	General population and no

Reference	Reason for exclusion
	subgroup analysis
SCHACHTER 1984[1505]	Wrong definition of Phys Dx – no objective test.
SCHAPER 2010[1508]	Wrong definition of Phys Dx – no objective test.
SCHERNHAMMER 2008[1512]	Wrong definition of Phys Dx – no objective test.
SCHOLTENS 2009[1523]	General population and no subgroup analysis
SCHOLTENS 2009A[1525]	General population and no subgroup analysis
SCHOLTENS 2010[1524]	General population and no subgroup analysis
SCHONBERGER 2004[1526]	Meets all inclusion criteria for prognostic study, but wrong follow-up time: >5 years. Children with wheeze followed for development of asthma in adolescence.
SCHUMPERT 2006[1528]	Wrong definition of Phys Dx – no objective test.
SCOTT 2010[1534]	Wrong definition of Phys Dx – no objective test.
SEARS 1996[1538]	Prevalence in General population and no subgroup analysis. Looks at the wrong risk factors (not those specified in our protocol).
SENNHAUSER 1995[1544]	Wrong definition of Phys Dx – no objective test.
SENTHILSELVAN 1993[1545]	Wrong definition of Phys Dx – no objective test.
SHAHEEN 1998[1551]	General population and no subgroup analysis
SHAHEEN 1999[1549]	General population and no subgroup analysis
SHAHEEN 2005[1547]	General population and no subgroup analysis
SHAHEEN 2000[1550]	General population and no subgroup analysis
SHAHEEN 2002[1548]	Prevalence of wheeze in future wheezers vs. non-wheezers (wrong comparison group).
SHANKARDASS 2009[1553]	General population and no subgroup analysis
SHAVIT 2007[1557]	Wrong definition of Phys Dx –

Reference	Reason for exclusion
	no objective test.
SHERRIFF 2009[1559]	General population and no subgroup analysis
SHIN 2010[1564]	Good definition of Phys Dx – uses objective test. BUT wrong comparison group: asthma vs. healthy controls, not other respiratory symptoms.
SHREWSBURY 2000[1571]	Meta-analysis of Tx studies – shows symptoms in asthma only (no comparison group).
SIBBALD 1992[1572]	General population and no subgroup analysis
SILVER 1998[1576]	Wrong definition of Phys Dx – no objective test.
SILVERS 2009[1577]	General population and no subgroup analysis; and looks at the wrong risk factors (not those specified in our protocol).
SILVERS 2012[1578]	Looks at the wrong risk factors (not those specified in our protocol).
SIMPSON 2010[1590]	Prevalence in General population and no subgroup analysis. Looks at the wrong risk factors (not those specified in our protocol).
SIN 2002[1594]	Wrong definition of Phys Dx – no objective test.
SISTEK 2001A[1600]	Wrong definition of Phys Dx – no objective test.
SISTEK 2006[1601]	Reference standard does not match protocol – asthma Dx based on questionnaire responses to doctor diagnosed asthma and attack in the last 12 months (no mention of objective test)
SMIT 2009[1609]	Does not give prevalence of symptoms.
SNIJDERS 2007[1617]	Looks at the wrong risk factors (not those specified in our protocol).
SOCKRIDER 2001[1619]	Wrong definition of Phys Dx – no objective test.
SOLOMON 2003[1620]	General population and no subgroup analysis

Reference	Reason for exclusion
SONNENSCHEIN 2012[1624]	Looks at the wrong risk factors (not those specified in our protocol).
SONNENSCHEIN VAN DER VOORT 2012[1623]	General population and no subgroup analysis
SORIANO 2003[1629]	All asthma pts – no comparison group; does not give prevalence of symptoms.
SOTIR 2006[1630]	Prevalence of asthma and wheeze in RTI pts, not symptoms in asthma.
SOTORAMIREZ 2013[1631]	Wrong definition of Phys Dx – no objective test.
SPEEVANDERWEKKE 1998[1638]	General population and no subgroup analysis
SPYCHER 2008[1646]	General population and no subgroup analysis
SPYCHER 2009[1648]	General population and no subgroup analysis
SPYCHER 2012[1647]	Wrong definition of Phys Dx – no objective test.
STERN 2008[1658]	Wrong definition of Phys Dx – no objective test.
STINGONE 2008[1662]	Asthma and no comparison group.
STINGONE 2011[1663]	Asthma and no comparison group.
STODDARD 1995[1664]	General population and no subgroup analysis
STRACHAN 1985[1668]	General population and no subgroup analysis
STRACHAN 1988A[1669]	Wrong definition of Phys Dx – no objective test.
STRACHAN 1994[1670]	Wrong definition of Phys Dx – no objective test.
STRACHAN 1996[1672]	Unclear definition of diagnosis – seems like self-reported.
STRACHAN 1996B[1671]	Wrong definition of Phys Dx – no objective test.
STRUNK 2002[1674]	RFs for night-awakening due to asthma, not for asthma. Prevalence of symptoms in people with asthma but no comparison group.
SUN 2011[1681]	General population and no subgroup analysis. Looks at the wrong risk factors (not

Reference	Reason for exclusion
	those specified in our protocol).
SUN 2013[1680]	General population and no subgroup analysis. Looks at the wrong risk factors (not those specified in our protocol).
SUNYER 2004[1683]	Wrong outcomes: fraction of asthma caused by atopy.
SUTHERLAND 2007[1685]	Wrong definition of Phys Dx – no objective test.
TAGIYEVA 2010[1695]	General population and no subgroup analysis
TAI 2009[1696]	General population and no subgroup analysis
TAKENOUE 2012[1700]	Meta-analysis of the influence of NO in the Dx of asthma.
TAN 2013[1705]	Wrong population: prevalence in obstructive airways combined, not asthma separated.
TAUSSIG 2003[1715]	Review of a study (TUSCON study).
TAVERAS 2006[1716]	Correct definition of Phys Dx, but looks at the wrong risk factors (not those specified in our protocol).
TAYLOR 1983[1717]	General population and no subgroup analysis
TAYLOR 2005[1718]	Wrong definition of Phys Dx – no objective test.
THOMAS 2010[1730]	Wrong definition of Phys Dx – no objective test.
THOMSON 2012[1732]	General population and no subgroup analysis
THORNE 2005[1734]	Looks at the wrong risk factors (not those specified in our protocol). Does not give prevalence in asthma vs. other respiratory diseases.
TIMONEN 2002[1739]	Wrong definition of Phys Dx – no objective test (older children).
TO 2004[1743]	Wrong definition of Phys Dx – no objective test.
TO 2009[1741]	Looks at the wrong risk factors (not those specified in our protocol). Does not give

Reference	Reason for exclusion
	prevalence in asthma vs. other respiratory diseases, only in general population.
TO 2012A[1742]	Wrong definition of Phys Dx – no objective test.
TOLLERUD 1991[1749]	Wrong definition of Phys Dx – no objective test.
TOLPPANEN 2013[1750]	General population and no subgroup analysis
TOOP 1985[1754]	Wrong definition of Phys Dx – no objective test.
TOREN 1993[1755]	Literature review.
TORRENT 2007[1757]	Wrong definition of Phys Dx – no objective test.
TROMP 2012[1767]	Looks at the wrong risk factors (not those specified in our protocol).
TSE 1993[1769]	Wrong definition of Phys Dx – no objective test.
TURBYVILLE 2011[1779]	Wrong definition of Phys Dx – no objective test.
TURCOTTE 2003[1780]	Prevalence and sens/spec in general population of athletes vs. controls (not suspected asthma, or asthma vs. other respiratory diseases).
TURNER 2008[1785]	Wrong symptoms: rattles, purrs, and whistles.
TURNER 2010A[1786]	General population and no subgroup analysis
TURNERWARWICK 1988[1787]	Prevalence in people with asthma, but no comparison group.
VALERY 2001[1794]	Not UK-relevant population.
VALERY 2004[1795]	Older children: looks at the wrong risk factors (not those specified in our protocol). Younger children: no comparison group (just prevalence in asthma)
VANBEVER 1999[1799]	Wrong population: croup and not compared with people without asthma.
VANDERGUGTEN 2012[1801]	General population and no subgroup analysis
VANDERMARK 2014[1802]	Longitunial study – symptoms

Reference	Reason for exclusion
	occurring aged 1-5 years as a predictor for asthma at 6 years
VANDERVALK 2012B[1809]	General population and no subgroup analysis
VANDERVALK 2013[1810]	General population and no subgroup analysis
VANDEVEN 2006[1800]	General population and no subgroup analysis
VANGENT 2007[1813]	Wrong definition of Phys Dx – no objective test (older children).
VANGYSEL 2007[1814]	General population and no subgroup analysis
VANMAANEN 2013[1815]	Wrong definition of Phys Dx – no objective test.
VANNIMWEGEN 2011[1816]	General population and no subgroup analysis
VANSCHAYCK 1991[1819]	Meets all inclusion criteria for prevalence study except sample size is N<200.
VANSCHAYCK 2000[1818]	Does not give the specific symptoms in the asthma subgroup.
VANZAANE 2007[1820]	Validation of a questionnaire; but does not give prevalence of symptoms in subgroup with asthma.
VARGAS 2007[1825]	Only gives data for the asthma group (no comparison group).
VEDAL 1998[1829]	Wrong definition of Phys Dx – no objective test.
VELLINGA 2005[1830]	Wrong definition of Phys Dx – no objective test.
VENABLES 1993[1832]	Sens/spec in general population; symptoms in asthma vs. control (wrong comparison group).
VENN 2000[1833]	General population and no subgroup analysis; Looks at the wrong risk factors: (not those specified in our protocol).
VENN 2001[1834]	Risk factors for wheeze, not asthma (in mostly older children).
VIALDUPUY 2011[1840]	Wrong definition of Phys Dx – no objective test.

Reference	Reason for exclusion
VOGELMEIER 2011[1849]	Post-Tx symptoms.
VOLKMER 1995[1851]	General population and no subgroup analysis
VONEHRENSTEIN 2000[1854]	General population and no subgroup analysis
VONMUTIUS 1999[1855]	Looks at the wrong risk factors: (not those specified in our protocol).
VUGT 2012[1860]	Gives prevalence in people with obstruction, but does not subgroup into asthma or COPD etc.
WAKE 2013[1862]	General population and no subgroup analysis
WANG 2008[1869]	Wrong definition of Phys Dx – no objective test.
WANG 2008A[1867]	General population and no subgroup analysis
WANG 2010[1868]	Wrong definition of Phys Dx – no objective test.
WASSALL 2005[1876]	Wrong definition of Phys Dx – no objective test.
WATELET 2010[1877]	Looks at the wrong risk factors: chronic cough (for the development of concomitant asthma).
WEINMAYR 2007[1882]	Wrong definition of Phys Dx – no objective test.
WEINMAYR 2013[1881]	Prevalence in General population and no subgroup analysis.
WHITROW 2010[1889]	Wrong definition of Phys Dx – no objective test.
WICKENS 2005[1890]	Wrong definition of Phys Dx – no objective test.
WICKENS 2008[1891]	Prevalence in General population and no subgroup analysis.
WIJGA 2003[1894]	Prevalence in general population and no subgroup analysis. Prevalence of asthma in wheezers, not prevalence of wheeze in people with asthma.
WILLERS 2007[1897]	General population and no subgroup analysis; and looks

Reference	Reason for exclusion
	at the wrong risk factors: (not those specified in our protocol).
WILLERS 2008[1898]	Wrong definition of Phys Dx – no objective test.
WITHERS 1998[1903]	Wrong definition of Phys Dx – no objective test.
WJST 1994[1906]	Wrong definition of Phys Dx – no objective test.
WJST 1998[1908]	Wrong definition of Phys Dx – no objective test.
WJST 2001[1907]	General population and no subgroup analysis; and looks at the wrong risk factors: (not those specified in our protocol).
WOLF 2003A[1910]	Wrong definition of Phys Dx – no objective test.
WOODS 2000[1917]	General population and no subgroup analysis; and looks at the wrong risk factors: (not those specified in our protocol).
WOODS 2001[1918]	General population and no subgroup analysis
WOODS 2001A[1916]	Wrong outcomes: predictors of breathlessness or food allergy intolerance in adults, not asthma.
WOODS 2002[1919]	General population and food allergies, no asthma subgroup analysis
WRIGHT 2001[1921]	General population and no subgroup analysis
WRIGHT 2006[1922]	Wrong definition of Phys Dx – no objective test.
WUTHRICH 1995[1924]	General population and no subgroup analysis
YEATTS 2000[1934]	Wrong definition of Phys Dx – no objective test.
YEATTS 2000A[1933]	Prevalence in subgroup with asthma, but no comparison group.
YEATTS 2003[1935]	General population and no subgroup analysis and looks at the wrong risk factors: (not those specified in our protocol).

Reference	Reason for exclusion
YUNGINGER 1992[1944]	Dx sens/sepc data: wrong population – general population. Prevalence data: wrong compariuson group – asthma vs. probable asthma or single episode wheezers.
ZHOU 2013[1955]	General population and no subgroup analysis
ZOLLNER 2005[1967]	General population and no subgroup analysis
ZUIDGEEST 2008[1968]	Wrong definition of Phys Dx – use of asthma medication to indicate asthma.
ZUIDGEEST 2009[1969]	Looks at the wrong risk factors: (not those specified in our protocol). Prevalence in asthma but no comparison group.
ZWAR 2011[1971]	Correct Phys Dx but does not give prevalence of symptoms in the asthma vs. COPD groups and does not look at the correct RFs (not those specified in our protocol).

K.2 Diagnosis: History of atopic disorders

Table 210: Studies excluded from the clinical review

Reference	Reason for exclusion
ALBUQUERQUE2013[34]	Conference abstract
ALVAREZPUEBLA 2002[39]	Index test does not match protocol – total asthma symptoms questionnaire, not history of atopic disorders
ANDERSON 2009[48]	Index test does not match protocol – history of atopic disorders not reported
BACKER 1991[88]	Reference standard does not match protocol – Dx made on the basis of questionnaire
BACKER 2014[92]	Index test and reference standard do not match protocol – sn/sp of FeNO to predict positive mannitol in suspected asthma (not physician diagnosis and objective test)
BEAUSOLEIL 2007[135]	Review article
BEEH 2000[138]	No relevant outcomes – prevalence in allergic vs non-allergic patients
BEEH 2001[139]	Index test does not match protocol – atopy defined as family history or positive SPT (cannot calculate the sn/sp of family history

Reference	Reason for exclusion
	alone)
BEEH 2004[140]	Index test does not match protocol – total symptom score with no breakdown of atopy history alone
BENGASHIR 2004[149]	Population does not match protocol – all patients positive for atopic dermatitis (all positive for index test)
BOCCACCINO 2007[183]	Population does not match protocol - patients with respiratory symptoms picked up using a screening questionnaire
BONNER 1984[190]	Review article
BREGAS 2000[222]	Not in English
BURR 1975[249]	No relevant outcomes and does not match review question – cannot calculate sn/sp of family history
CAFFARELLI 2005[260]	Population does not match protocol – all patients positive atopic eczema (all positive for index test)
CANTANI 2003[268]	Reference standard does not match protocol – no objective test
CARTER 2000[285]	No relevant outcomes and does not match review question - sn/sp of patients report of allergy for positive SPT in people with confirmed asthma
CHEN 2014[307]	Population does not match protocol – general population
CHRISTOFF 2013[324]	Conference abstract
CIRILLO 2003[337]	Population does not match protocol – general population
CORTESALVAREZ 2007[363]	Reference standard does not match protocol – history of atopic disorders in ≤ 3 yrs with wheezing, but no Dx of asthma made
CVITANOVIC 2007[383]	Population does not match protocol – all SPT positive.
DEBLEY 2012[404]	Population does not match protocol – children aged 4-36 months with ≥3 episodes of physician Dx wheezing (all people with asthma according to protocol criteria)
DELRIO 2004[410]	Case-control study – asymptomatic and symptomatic patients.
DELIU 2013[414]	Conference abstract
DENG 2010[419]	Population does not match protocol - patients with respiratory symptoms picked up using a screening questionnaire, not presenting to GP
DING 2012[439]	Population does not match protocol - patients with respiratory symptoms picked up using a screening questionnaire

Reference	Reason for exclusion
ELIZUR 2007[470]	No relevant outcomes and does not match review question – prevalence study in general population
ERIKSSON 1978[475]	Population does not match protocol – all asthma and/or rhinitis
ERIKSSON 1990[476]	Population does not match protocol – all asthma and/or rhinitis
EYSINK 2005[482]	Case-control study – IgE positive and IgE negative
FANIRAN 1998[484]	Index test does not match protocol – sn/sp of first Dx by a physician in primary healthcare
FARHOUDI 2005[487]	Population does not match protocol – allergic patients with asthma and/or rhinitis
FONSECA 2004[501]	Population does not match protocol – not suspected asthma only, population consisted of people with confirmed asthma
FRANK 1998[513]	Population does not match protocol – general population
GALVEZ 1987[537]	Reference standard objective test does not match protocol – methacholine challenge test positive defined as PC20 <25mg/ml.
GUILBERT 2004[607]	Population does not match protocol – all had a personal or family history of atopic disorders
GULSVIK 1979[609]	No relevant outcomes – prevalence of symptoms in the general population
GUSTAFSSON 2000[611]	Population does not match protocol – children with atopic dermatitis
HAFKAMPDEGROEN 2013[615]	Longitudinal prognostic study
HEDMAN 1998[647]	Index test does not match protocol – history of atopic disorders not reported
JENKINS 1996[764]	Index test does not match protocol – sn/sp of symptoms questionnaire. Reference standard does not match protocol – Dx based on a history of wheeze in the past 12 months
KARAKAYA 2012[816]	No relevant outcomes – sn/sp of physician Dx of atopy with SPT as the gold standard
KILPELAINEN 2001B[857]	Index test does not match protocol – sn/sp of symptoms questionnaire
KUMAR 2010[929]	No relevant outcomes – allergy Dx in patients with asthma or allergic rhinitis
KUMARI 2006[931]	Case-control study – atopic and non-atopic patients
LOMBARDI 2008[1026]	No relevant outcomes – prevalence of asthma and allergy in general population
LOMBARDI 2011[1025]	No relevant outcomes – prevalence of asthma and allergy in general population

Reference	Reason for exclusion
MILLER 2007[1141]	Population does not match protocol – general population
MONTNEMERY 2002[1162]	Index test does not match protocol – sn/sp of first Dx of asthma in primary healthcare
NANTANDA 2013[1197]	Popultation does not match protocol – includes severe asthma and >50% <12 months old.
NJA 2001[1240]	Case-control study. Reference standard does not match protocol – Dx made on the basis of symptoms, no objective test
NINAN 1995[1235]	Case-control study – asymptomatic and symptomatic patients. Reference standard does not match protocol – Dx made on the basis of symptoms
PEDROSA 2009[1315]	No relevant outcomes – cannot calculate sn/sp of family history
RIEDLER 1994[1444]	Case control study
RUGINA 2002[1475]	No relevant outcomes - prevalence of symptoms in nasal polyposis
SCHLEICH 2012[1514]	Index test does not match protocol – FeNO and symptoms
SMITH 2009[1615]	Population does not match protocol – all currently Dx with rhinitis or asthma
SNIDER 1985[1616]	Review article
STAIKUNIENE 2008[1653]	Case-control study - chronic rhinosinusitis vs controls
TIMONEN 1997[1738]	Population does not match protocol - patients with chronic respiratory symptoms picked up using a screening questionnaire
VALERY 2003[1796]	Case-control study. Index test does not match protocol – sn/sp of symptoms questionnaire
WOO 2012[1914]	Index test does not match protocol - FeNO
ZARAGOZA 2014[1949]	Conference abstract

K.3 Diagnosis: Symptoms after exercise

Table 211: Studies excluded from the clinical review

Reference	Reason for exclusion
ANDERSON 2009[48]	Index test does not match protocol.
ANDERSON 2010A[46]	Conference abstract
ANTOLINAMERIGO 2012[54]	Conference abstract
BRANNAN 1998[218]	No relevant outcomes and does not match

Reference	Reason for exclusion
	review question (sensitivity and specificity of mannitol challenge test to predict EIA in participants with a positive response to exercise challenge test or eucapnic hyperventilation).
BROZEK 2009[234]	Conference abstract. Index test does not match protocol (exercise challenge test)
CARLSEN 2000[274]	No relevant outcomes and does not match review question (comparing methods of exercise challenge test in people with confirmed asthma with exercise-induced bronchoconstriction)
CHEW 1999[309]	Reference standard does not match protocol (asthma Dx made on the basis of the question 'have you (your child) ever had asthma?')
CHINELLATO 2012[312]	Population does not match protocol – all people with asthma on treatment
DEMISSIE 1998[416]	Population does not match protocol (general population, not suspected asthma); index test does not match protocol (general symptom questions, not symptoms after exercise); reference standard does not match protocol (Dx by questionnaire)
DRYDEN 2010[453]	Review including 2 studies with exercise symptoms as the index test (population does not match protocol for both studies – general population of athletes, not suspected asthma)
FOUCARD 1984[507]	Reference standard does not match protocol (children who reported asthma symptoms during the last year were regarded as having asthma)
FUENTES 2011[525]	Case control study. Reference standard for Dx in the group with asthma does not match protocol (no mention of objective test) so cannot use index test vs exercise challenge test.
GREEN 1997[589]	No relevant outcomes and does not match review question (cannot calculate sensitivity and specificity of 'symptoms in response to exercise' in the Dx of asthma).
HETLEVIK 2000[666]	Reference standard does not match protocol (current asthma Dx if affirmative response to the question 'has your child ever had asthma?' and 'does your child still have asthma?')
HILDEBRAND 2011[671]	Not in English
JONES 1994[774]	Reference standard does not match protocol (not all had objective test)
JOSEPH 1999[781]	Reference standard does not match

Reference	Reason for exclusion
	protocol (self-reported physician Dx of asthma – no objective test).
KERSTEN 2009[844]	Index test does not match protocol – exercise challenge test not history of symptoms with exercise
KIVILOOG 1975[871]	Reference standard does not match protocol - all people with confirmed asthma and possible to calculate test vs test (sn/sp of IT in detecting positive exercise challenge) but no mention of how asthma Dx was made (no mention of objective test).
LAI 1997[948]	Reference standard does not match protocol
LEX 2007[995]	Index test does not match protocol – sn/sp of symptoms to detect EIB in people with asthma but includes symptoms induced by exercise and other factors such as allergy, no breakdown of those who only had symptoms to exercise
LOWHAGEN 1999[1030]	Review article checked for references
LUKRAFKA 2010[1034]	Reference standard does not match protocol, no objective test (asthma Dx based on affirmative answer to 'Have you ever been told by a physician that you have asthma or bronchitis?')
MAJAK 2013[1055]	Population does not match protocol (groups with and without a history of exercise symptoms, but group without symptoms in response to exercise included patients whose asthma was in remission).
MANSOURNIA 2007[1075]	Target condition does not match protocol - sn/sp of exercise symptoms to Dx EIB in the general population
NEVILLE 1992[1212]	No relevant outcomes and does not match review question (prevalence of symptoms in general population)
PEDROSA 2009[1315]	Index test does not match protocol – cannot calcultate sn/sp of index test in Dx of asthma.
PONSONBY 1996[1363]	Population does not match protocol – general population (including healthy asymptomatic children) not suspected asthma alone
RANDOLPH 1997[1416]	Population does not match protocol – general population (including healthy asymptomatic children) not suspected asthma alone
RANDOLPH 2011A[1417]	Conference abstract
RANDOLPH 2012[1419]	Conference abstract
RANDOLPH 2013[1418]	Conference abstract

Reference	Reason for exclusion
REMES 2002 [1433]	Population does not match protocol – general population (including healthy asymptomatic children) not suspected asthma alone
SEEAR 2005[1540]	No relevant outcomes and does not match review question (exercise challenge test to determine the accuracy of EIA Dx)
SIERSTED 1996[1574]	Index test does not match protocol
SINCLAIR 1995[1595]	Index test does not match protocol – exercise challenge test not history of symptoms with exercise
SMEETON 2006[1608]	No relevant outcomes and does not match review question (prevalence of symptoms in general population)
STORMS 2000[1666]	Review article
TERBLANCHE 1990[1722]	Index test does not match protocol – exercise challenge test not history of symptoms with exercise
TERNESTENHASSEUS 2008[1724]	No relevant outcomes and does not match review question (gives levels and changes after exercise test, cannot calculate sn/sp)
TSYBULKINA 2009[1775]	Conference abstract
WEST 1996[1886]	Index test and reference standard do not match protocol
ZIAEE 2009[1956]	Conference abstract

K.4 Diagnosis: Symptoms after using medication

Table 212: Studies excluded from the clinical review

Reference	Reason for exclusion
AHMETAJ 2009[25]	Not addressing review question (prevalence of aspirin-sensitive asthma using challenge test in people with confirmed asthma)
ALONSO 2002[38]	Not addressing review question (diagnostic accuracy of challenge test vs. physician Dx of aspirin-induced asthma)
AMEISEN 1985[42]	Wrong population (asthma vs. healthy controls). Wrong study type (case control)
BARLES 1988[109]	Wrong population (all aspirin-sensitive asthma patients). Not Dx of asthma
BARRANCO 2009[114]	Not addressing review question (aspirin challenge test to diagnose aspirin-sensitive asthma in people with confirmed asthma)
BAVBEK 2010[132]	Conference abstract. Not addressing review question (prevalence of aspirin-sensitive asthma in people with confirmed asthma)

Reference	Reason for exclusion
BAVBEK 2012[131]	Not addressing review question (index test as a predictor of aspirin-sensitive asthma in people with confirmed asthma, not for asthma Dx)
BERGES 2002[159]	Wrong population (all aspirin-sensitive asthma patients). Not Dx of asthma
BOTEY 1988[199]	Wrong population (all people with asthma)
CALADO 2011[262]	Conference abstract. Full paper (CALADO 2012) obtained
CALADO 2012[263]	Non-English language publication (Portuguese)
CARNIMEO 1981[278]	Not addressing review question (index test as a predictor of positive aspirin challenge test not for asthma Dx)
CASADEVALL 2000[288]	Wrong population (asthma vs. healthy controls). Wrong study type (case control)
CASTILLO 1986[290]	Wrong population (all asthma patients)
CHANG 2011[298]	Not addressing review question (diagnostic accuracy of index test as a predictor of AERD in people with confirmed asthma, not for asthma Dx)
CROCE 1992[374]	Wrong population (asthma vs. healthy controls). Wrong study type (case control)
DAHLEN 1990[385]	Not addressing review question (aspirin challenge test to diagnose aspirin-sensitive asthma in people with confirmed asthma)
DELANEY 1976[412]	Not addressing review question (index test as a predictor of positive aspirin challenge test not for asthma Dx)
GENTON 1985[549]	Wrong population (asthma or urticarial)
GONZALEZ 2011[581]	Wrong population (all asthma patients)
GRZELEWSKA 1981[598]	Not addressing review question (index test as a predictor of aspirin-sensitive asthma)
HONG 1989[689]	Wrong population (all asthma patients)
HUSSEIN 1989[717]	Not addressing review question (index test as a predictor of positive aspirin challenge test not for asthma Dx)
KARAKAYA 2000[814]	No comparison with reference standard
MAKOWSKA 2008[1056]	Not addressing review question (aspirin challenge test to diagnose aspirin-sensitive asthma in people with confirmed asthma)
MASCIA 2005[1084]	Index test vs. objective test but does not give the number of patients +ve/-ve for objective test so sensitivity and specificity of IT cannot be calculated

Reference	Reason for exclusion
MELILLO 1991[1119]	Not addressing review question (index test as a predictor of positive aspirin challenge test not for asthma Dx)
MILEWSKI 1998[1138]	Wrong population (asthma vs. healthy controls). Wrong study type (case control)
MILLER 2013[1140]	Not addressing review question (challenge test to diagnose AERD in people with asthma)
MIRAKIAN 2012[1145]	Wrong population (all aspirin-sensitive asthma patients). Not Dx of asthma
MUNOZ 2013[1180]	Wrong population (patients with aspirin-sensitive asthma)
NIKLAS 1973[1221]	Wrong population (all asthma patients with no history of symptoms to aspirin)
NIZANKOWSKA 2000[1239]	Not addressing review question (aspirin challenge test to diagnose aspirin-sensitive asthma in people with confirmed asthma)
RACHELEFSKY 1975[1405]	Not addressing review question (prevalence of aspirin-sensitive asthma using challenge test in people with confirmed asthma)
RAM 2013[1410]	Wrong outcomes (not Dx of asthma)
RAMIREZ 2011[1412]	Not addressing review question (reliability study of provocation test – not Dx of asthma)
STENIUS 1976[1656]	Not addressing review question (prevalence of aspirin-sensitive asthma using challenge test in people with confirmed asthma)
SUETSUGU 1981[1678]	Wrong population (all aspirin-sensitive asthma patients)
VAIDYANATHAN 2012[1792]	Conference abstract. Not addressing review question (index test as a predictor of positive aspirin challenge test not for asthma Dx)
WEBER 1979[1878]	Wrong population (all asthma patients)
WISMOL 2012[1902]	Wrong population (all aspirin-sensitive asthma patients). Not Dx of asthma
ZAMBONINO 2013[1948]	Conference abstract. Not addressing review question (index test not used for asthma Dx)

K.5 Diagnosis: Occupational asthma

Table 213: Studies excluded from the clinical review

Reference	Reason for exclusion
ANEES2003[51]	Not asking if symptoms better away from work
ARCHAMBAULT 2001[62]	Not all patients had gold standard test
BALDWIN 2002[97]	Not asking if symptoms better away from work
BARBER 2007[108]	Survey of diagnostic approach to single case scenario, not diagnostic value of asking if symptoms better away from work
BERNSTEIN 1993[162]	Not all patients had gold standard test
BLANC 1996[180]	Not asking if symptoms better away from work
CAMPBELL 2007[266]	Not asking if symptoms better away from work
CARTIER 2003[287]	No usable data
COTE 1990[365]	Only includes people with positive history so cannot calculate specificity
COTE 1993[366]	Not asking if symptoms better away from work
CRESPO 2001[373]	Not asking if symptoms better away from work
CRUZ 2010[375]	Not asking if symptoms better away from work
DELLABIANCA 1996[415]	Not asking if symptoms better away from work
DESCATHA 2005[426]	Not asking if symptoms better away from work
DOSTALER 2011[445]	No gold standard for occupational asthma, only questionnaire development
DUCE 1988[456]	Not asking if symptoms better away from work
ELSHABRAWI 2011[472]	Not asking if symptoms better away from work
ENARSON 1988[473]	Not asking if symptoms better away from work
GAUTRIN 2010[547]	Not asking if symptoms better away from work
GIRARD 2004[566]	Not asking if symptoms better away from work
GORDON 1997[582]	Not asking if symptoms better

Reference	Reason for exclusion
	away from work
GRAMMER 1992[587]	Not asking if symptoms better away from work
GRAMMER 1998[586]	Not asking if symptoms better away from work
HANNU 2013[631]	Not asking if symptoms better away from work
HAYATI 2008[643]	Not asking if symptoms better away from work
HAYATI 2006[642]	Not asking if symptoms better away from work
HUR 2008[715]	Reference standard is for diagnosis of occupational asthma or occupational eosinophilic bronchitis
JARES 2012[757]	No usable data
KARVALA 2010[819]	Not asking if symptoms better away from work
KIM 1998[859]	Not occupational asthma
KONGERUD 1992A[899]	All participants positive for history and bronchial challenge test
KRAW 1999[918]	Not asking if symptoms better away from work
LABRECQUE 2011[944]	Not asking if symptoms better away from work
LEMIERE 1999[980]	Not asking if symptoms better away from work
LEMIERE 2011[978]	Not asking if symptoms better away from work
LEMIERE 2011A[979]	Not asking if symptoms better away from work
LIPINSKA 2011[1017]	Not asking if symptoms better away from work
MALO 1993[1066]	Not asking if symptoms better away from work
MALO 1995[1069]	Not asking if symptoms better away from work
MERGET 1991[1124]	Not asking if symptoms better away from work
MIEDINGER 2013[1132]	Not asking if symptoms better away from work
MIRMOHAMMADI 2010[1147]	Assesses a questionnaire but asking if symptoms better away from work was not part of the definition of questionnaire-positive responses
MOORE 2009[1165]	Not asking if symptoms better

Reference	Reason for exclusion
	away from work
MOORE 2010[1164]	Not asking if symptoms better away from work
MOSCATO 1993[1169]	Not asking if symptoms better away from work
MURPHY 2002[1182]	Not asking if symptoms better away from work
NASIR 2011[1199]	Not asking if symptoms better away from work
OLAGUIBEL 1989[1267]	Not asking if symptoms better away from work
PERRIN 1992[1323]	Not asking if symptoms better away from work
PHAKTHONGSUK 2007[1341]	Not assessing asking if symptoms better away from work versus gold standard
QUIRCE 1995[1404]	Not asking if symptoms better away from work
SCHLUNSSEN 2011[1515]	Not asking if symptoms better away from work
SCHWAIBLMAIR 1997[1529]	Not asking if symptoms better away from work
SHOFER 2006[1567]	Not asking if symptoms better away from work
SKOVSTED 2003[1604]	Not asking if symptoms better away from work
SMITH 1987[1610]	Not asking if symptoms better away from work
STENTON 1993[1657]	Not asking if symptoms better away from work
SUARTHANA 2010[1676]	Outcome is wheat sensitisation not asthma
SURANGE 2011[1684]	Single case report not diagnostic test value
TALINI 2002[1702]	Not asking if symptoms better away from work
TARLO 1991[1709]	Not asking if symptoms better away from work
TARLO 2000[1710]	not all participants had gold standard test
TARLO 2008[1711]	Not assessing asking if symptoms better away from work versus gold standard
TARLO 2009[1712]	Not assessing asking if symptoms better away from work versus gold standard

Reference	Reason for exclusion
TEE 1998[1719]	Not asking if symptoms better away from work
TORRESDA 2002[1758]	non-English
TURNER 2010[1784]	Not asking if symptoms better away from work
VOGELMEIER 1991[1848]	Not asking if symptoms better away from work
WIESLANDER 1994[1893]	Not asking if symptoms better away from work
WITTCZAK 2012[1904]	Not asking if symptoms better away from work
WHITE 2013[1888]	General population
HATHAWAY 2014[641]	General population
WALTERS 2012A[1866]	General population
KAYHAN 2013[828]	General population

K.6 Diagnosis: Spirometry

Table 214: Studies excluded from the clinical review

Reference	Reason for exclusion
AHFMR 2002[30]	Full article not available
ALBERTS 1994[32]	Index test does not match protocol – sn/sp of FEF25-75%
BROUWER 2010[233]	Index test does not match protocol – sn/sp of PEFv and FEV1 variation for Dx of asthma
BUFFELS 2012[242]	Reference standard does not match review protocol – Dx with spirometry taken as reference.
CERVERI 2009[295]	No relevant outcomes - sn/sp of FEV1/FVC in predicting airflow obstruction with lower limit of normality as gold standard in people with confirmed asthma
CIPRANDI 2010[333]	Population does not match protocol – all people with asthma or rhinitis. Index test does not match protocol – FeNO
CIPRANDI 2011B[332]	Population does not match protocol – all Dx with allergic rhinitis and excluded if a history of asthma or referred with asthma symptoms
CIPRANDI 2011C[329]	Population does not match protocol – patients with allergic rhinitis; exclusion criteria was previous asthma Dx or presence of asthma symptoms.
CIPRANDI 2012[330]	No relevant outcomes - sn/sp of FEV1 or FVC in predicting airways obstruction with FEF25-75% as gold standard in people with confirmed asthma

Reference	Reason for exclusion
CIRILLO 2006[335]	No relevant outcomes – association between positive MCT and the ratio between FEV1 and FEF25-75%
CORDEIRO 2011[360]	No relevant outcomes – cannot calculate the sn/sp of FEV1/FVC for asthma Dx. Only gives ROC AUC for FEV1/FVC
COUTO 1997[368]	Index test does not match protocol - MCT
DI LORENZO 2007[432]	Case control study – study gives sn/sp values for FEV1/FVC, but this includes asymptomatic healthy control group
DUNDAS 2006[459]	Review article
DUPONT 2003[460]	Index test does not match protocol - FeNO
DWYER 2012[462]	Review article
EID 2000[466]	No relevant outcomes – sn/sp of PEF to predict abnormal FEV1
FOWLER 2000[508]	Index test does not match protocol – MCT and correlation of FEV1 with MCT
FRANKLIN 2003[514]	Population does not match protocol – general population
FUKUHARA 2011[529]	Index test does not match protocol - FeNO
GALVEZ 1987A[536]	No relevant outcomes – correlation between FEV1 and PC20 in people with confirmed asthma
GERALD 2004[552]	Population does not match protocol – general population. Index test does not match protocol – sn/sp of procedures including symptoms questionnaire, spirometry and exercise test.
GILBERT 1985[563]	Target condition does not match protocol – sn/sp of FEV1/FVC to Dx obstruction (asthma and COPD) with reference standard of clinical and body plethysmographic data
GILBERT 1986[562]	Target condition and reference standard do not match protocol – Dx of obstuction based on history, physical examination, chest radiographs, biopsy and body plethysmographic data
GOEDHART 2006[572]	Case control type study – confirmed asthma and COPD. Reference standard does not match protocol – without objective test.
GRZELEWSKI 2014[600]	Study does not report results in such a way that it is possible to calculate sensitivity and specificity.
HARGREAVE 2009[634]	Review article
HEDENSTROM 1987[646]	Case control study – sn/sp of FEV1 in people with asthma vs healthy controls
HOLT 2006[683]	No relevant outcomes – comparing treatment plans made by physicians using symptoms alone or with spirometry

Reference	Reason for exclusion
HUNTER 2002[713]	Case control study – calculation of sn/sp in people with confirmed asthma, healthy controls and pseudoasthma, with no breakdown.
JERZYNSKA 2014[768]	Study does not report results in such a way that it is possible to calculate sensitivity and specificity.
KING 1998[865]	Case report
KOMAROW 2012[896]	Index test does not match protocol – impulse oscillometry or BDR
LAMBERT 2013[952]	Meeting abstract
LEBECQUE 1993[970]	No relevant outcomes – comparing different spirometry measures in people with confirmed asthma
LEHMANN 2008[976]	Population does not match protocol – general population
LIAM 2001[999]	No relevant outcomes - association between FEV1 and symptoms or BDR in people with confirmed asthma
LIM 2005[1004]	Review article
LINNA 1996[1012]	Population does not match protocol – all people with asthma and cannot calculate sn/sp of test vs test.
LIOU 2009[1016]	Review article
LUTFI 2011[1038]	Case-control study – people with confirmed asthma and healthy controls
MAGYAR 1998[1050]	Review article
MELBYE 2011[1117]	Population and reference standard does not match protocol – confirmed asthma, COPD and asthma+COPD. Reference standard for Dx not reported.
MELTZER 1989[1120]	No relevant outcomes- comparison of PEF and FEV1 in people with confirmed asthma
MENDONCA 2011[1121]	Case-control study. Asthma Dx with clinical Dx, no mention of objective test
MILLER 1990[1139]	No relevant outcomes – comparing different spirometry measures in people with confirmed asthma with normal FEV1/FVC
MINAKATA 2008[1143]	Population does not match protocol – presenting with diseases other than respiratory diseases
MIRAVITLLES 2012[1146]	No relevant outcomes – cannot calculate the sn/sp of spirometry for asthma
MODRYKAMIEN 2009[1155]	Target condition does not match protocol – sn/sp of spirometry to detect upper airway obstruction with reference standard of bronchoscopy, laryngoscopy and tomogram
NEVE 2012[1211]	Population does not match protocol –

Reference	Reason for exclusion
	preschool children aged 3-5 years old with wheezing disorders
NICOLAI 1993[1223]	Population does not match protocol – general populations. Index test does not match protocol – cold air challenge
NIKKHAH 2011[1233]	Case control study
OTTER 1997[417]	Index test does not match protocol
OZAREKHANC 2012[1280]	Article not in English
PEDROSA 2009[1315]	Population and index test do not match protocol – all patients normal spirometry and index test is challenge test
SATO 2008[1499]	Index test does not match protocol - FeNO
SAURO 2005[1501]	Populations does not match protocol – general population
SCHERMER 2000[1510]	Review article
SIMON 2010[1587]	All people with asthma (test vs test) – can calculate sn/sp of FEV1/FVC for detecting BDR. FEV1/FVC at 95% cut-off (best cut-off determined from ROC curve) for detecting BDR 20% increase in FEV1
SLIEKER 2003A[1607]	No relevant outcomes – sn/sp of PEF to predict abnormal FEV1 pre- and post-bronchodilator
STENTON 1993[1657]	Population does not match protocol – screening shipyard workers and job applicants
TEETER 1999[1720]	Review article
THIADENS 1999[1728]	No relevant outcomes – comparison of ΔPEF and ΔFEV1 for BDR
TINKELMAN 2006[1740]	Target condition does not match protocol – sn/sp of questionnaire in the Dx of COPD
TODA 2009[1744]	Index test does not match protocol – FEV1/FVC used as reference standard for obstruction
WALAMIES 1998A[1863]	Case control study. Index test vs comparator test in people with asthma – cut-off values do not match protocol (FEV1/FVC 89% and BDR ΔFEV1pred ≥15%
YARTSEV 2006A[1930]	Case- control study
YU 2004[1942]	Population does not match protocol – general populations. Reference standard does not match protocol – parental report of doctor Dx asthma.
YURDAKUL 2005[1945]	Case-control study. Index test does not match protocol

K.7 Diagnosis: Bronchodilator reversibility

Table 215: Studies excluded from the clinical review

Reference	Reason for exclusion
ADAMS 2003[17]	No data on bronchodilator response in diagnosed asthma group
BIBI 1991[172]	Wrong cut-off for FEV1: change >6%.
BIRING 2001[174]	Asthma and COPD together
BONINI 2007[188]	Not all participants had reference standard tests
BORREGO 2012[193]	Not in English
BORREGO 2013[196]	Not bronchodilator response over/under threshold versus asthma status
BOSSLEY 2009[198]	Number with bronchodilator response reported but not comparison/gold standard test
BUSSAMRA 2005[254]	Reference standard is the same test (bronchodilator response) with American Thoracic Society specified cut-off rather than 95th percentile cut off
CARLSEN 1995[273]	Case control study
CHOI 2007[315]	Bronchodilator response is part of gold standard (index test = questionnaire)
CIPRANDI 2011[332]	Allergic rhinitis patients not asthma
CIPRANDI 2011A[328]	Unavailable
CIPRANDI 2013[334]	Bronchial reversibility as gold standard (index test = FeNO)
CORDEIRO 2011[360]	Bronchial reversibility as part of gold standard (index test = FeNO)
CORSICO 2007[362]	Bronchial reversibility as part of asthma diagnosis (not all participants had this test)
COTE 1990[365]	Occupational asthma
DELRIO 2004[410]	Not bronchial reversibility versus doctor diagnosis (all had asthma) or versus other tests for diagnosis of asthma (symptomatic versus asymptomatic on ISAAC questionnaire)
DIAS 2010[433]	Not in English
DUMAS 2010[457]	Bronchodilator test was gold standard as well as index test
DUNDAS 2005[458]	Case control study
ELLIOTT 2013	Population does not match protocol – children less than 1 year old
FABBRI 2003[483]	Variability to inhaled albuterol part of gold standard as well as index test
FISH 1978[495]	Workshop not primary study
FRUCHTER 2009[524]	Not all participants had bronchodilator

	reversibility test; longitudinal follow up for later diagnosis of asthma
FRUCHTER 2009[523]	Correlation between PC20 and ΔFEV1 not reversibility over/under threshold versus postivie/negative methacholine challenge test
GALANT 2007[535]	Population does not match protocol – general population
GHARAGOZLOU 2004[555]	Not all participants had bronchodilator test
GIBSON 1995[558]	Not bronchodilator response
GINGO 2012[565]	Not bronchodilator reversibility versus doctor diagnosis or other test for asthma
GJEVRE 2006[567]	Subjects selected for meeting ATS bronchodilator response criteria
GOLDSTEIN 2001[580]	Longitudinal follow up for later diagnosis of asthma
GRIFFITHS 1999[593]	Bronchodilator reversibility = definition of asthma (gold standard not index test)
HELLINCKX 1998[653]	Not PEF, PEFR or FEV_1
HUNTER 2002[713]	Case-control study. Mixed population of cases, controls and pseudoathma in the results. Not separated out the data.
HYVARINEN 2006[719]	Not PEF, PEFR or FEV_1
IRWIN 1997[732]	Not PEF, PEFR or FEV_1
JAIN 2013[742]	Not bronchodilator reversibility versus doctor diagnosis or other test for asthma
JOSEPH 2011A[782]	Not bronchodilator reversibility versus doctor diagnosis or eligible comparator test for asthma
KESTEN 1994[845]	Lung function tests part of gold standard as well as index test
KJAER 2008A[872]	Case control study; bronchodilator test part of gold standard as well as index test
KONSTANTINOU 2010[900]	Longitudinal study: bronchodilator response during exacerbation compared with no exacerbation
KOWAL 2009[914]	Not bronchodilator reversibility versus doctor diagnosis or other test for asthma
LEHMANN 2008[976]	Bronchodilator reversibility = gold standard not index test; not shown versus doctor diagnosis of asthma or other comparator tests (only questionnaire symptoms or other measures of FEV1 or FVC)
LERDLUEDEEPORN 1999[984]	Not bronchodilator reversibility versus

	doctor diagnosis or other test for asthma
LINNA 1999[1012]	Not bronchodilator reversibility versus doctor diagnosis or other test for asthma
LORBER 1978[1028]	Wrong population – general population
MALMBERY 2003[1064]	Case control study
MEHRPARVAR 2013[1115]	Occupational asthma
MELE 2010[1118]	Not PEF, PEFR or FEV_1
MESLIER1989[1125]	Only reports change in FEV1 as % initial or absolute volume alone
MIRAVITLLES 2010[1146]	Bronchodilator test part of gold standard (doctor diagnosis) as well as index test
MUNNIK 2010[1179]	Bronchodilator test part of gold standard (doctor diagnosis) as well as index test
MUSK 2011[1185]	Not all participants had bronchodilator test
NOWAK 1996[1247]	Not all participants had bronchodilator test
OHKURA 2013[1262]	Conference abstract – have enough fully published data already
OOSTVEEN 2010[1271]	Age <5 years; not PEF, PEFR or FEV_1
PATON 2010[1306]	Not primary study
PEDROSA 2010[1316]	All participants selected for negative bronchodilator test
PETANJEK 2007[1332]	All participants selected for positive bronchodilator test
PINO 1996[1351]	Wrong outcome measure of FEV1 (Change in FEV1% >15% - not clinically relevant)
POSTMA 1995 [1370]	Longitudinal study – bronchodilator test and diagnosis not at the same time
PRUITT 2012 [1397]	Not primary study
REED 2010[1428]	Not primary study
RENWICK 1996 [1436]	Not all participants had bronchodilator test
RHEE 2013[1438]	Bronchodilator test part of gold standard (doctor diagnosis) as well as index test
RICHTER2008[1441]	Only reports change in FEV1 as % initial or absolute volume alone
ROBINSON 2010[1451]	Not bronchodilator reversibility versus doctor diagnosis or other test for asthma (same study as Robinson 2012 below)
ROBINSON 2012[1452]	Not bronchodilator reversibility versus doctor diagnosis or other test for

	asthma
RUPPEL 2012[1477]	Not a primary study
SALLAWAY 2011[1487]	Not all participants had bronchodilator test
SALOME 1999[1489]	Not all participants had bronchodilator test
SANCHEZ 2012[1490]	Participants selected for negative bronchodilator test
SANCHEZ 2013[1491]	Bronchodilator test part of gold standard not index test
SCHNEIDER 2013[1520]	Not all participants had bronchodilator test
SCOTT 2012[1535]	Not all participants had bronchodilator test
SILVESTRI 2008[1579]	Bronchodilator test part of gold standard (doctor diagnosis) as well as index test(from guidelines cited references 13 and 14: asthma info page 6 of asthma guideline and COPD info on p 11 of COPD guideline; both pdfs accessed from: http://www.jornaldepneumologia.com.br/detalhe_suplemento.asp?id=40 (in Portuguese)
SIN 2006[1592]	Bronchodilator test part of gold standard (doctor diagnosis) as well as index test
SINGH 2012[1597]	Not bronchodilator reversibility versus doctor diagnosis or other test for asthma
SLIEKER 2003[1607]	Not all participants had bronchodilator test
SMITH 2004[1613]	Bronchodilator test part of gold standard (doctor diagnosis) as well as index test
SOBOL 1985[1618]	Not bronchodilator reversibility versus doctor diagnosis or other test for asthma
SPOSATO 2008[1643]	Not bronchodilator reversibility versus doctor diagnosis or other test for asthma
THIADENS 1998A[1726]	Bronchodilator test as gold standard (doctor diagnosis) not index test
THIADENS 1999[1728]	Bronchodilator test as gold standard (doctor diagnosis) as well as index test
TOMITA 2013[1753]	Bronchodilator test part of gold standard (doctor diagnosis) not index test. Scoring system of signs and symptoms, algorithm based on BDR or reversibility.
TSE 2013[1770]	Case control study

ULRIK 2005[1789]	Wrong outcome measure of FEV1 (Change in FEV1% >10% - not clinically relevant)
VUGT 2012[1860]	Bronchodilator test used as gold standard as well as index test
WALAMIES 1998[1863]	Wrong cut-off value for FEV1: change ≥5%
WALRAVEN 2001[1865]	Not all participants had bronchodilator test
WARDMAN 1986[1874]	Not all participants had bronchodilator test
WOLFF 2012[1912]	Not all participants had bronchodilator test
YANG 2011A[1927]	Case control study; bronchodilator test part of gold standard (doctor diagnosis) not index test
YAO 2011[1929]	FeNO not bronchodilator response
YOO 2007[1937]	Not doctor diagnosed asthma; not bronchodilator reversibility versus doctor diagnosis or other test for asthma
ZWAR 2011[1971]	Not bronchodilator reversibility versus doctor diagnosis or other test for asthma

K.8 Diagnosis: PEF variability

Table 216: Studies excluded from the clinical review

Reference	Reason for exclusion
AGGARWAL2002[21]	Case control study
AITKHALED2006[26]	Not PEF over/under a certain threshold versus asthma status
ALBERTINI1989[31]	Case control study
ANEES2011[50]	Not PEF over/under a certain threshold versus asthma status
BARUA2005[118]	Not a primary study
BASER2007[119]	Not PEF versus another test for asthma (PEF included in the definition of asthma)
BECKETT2006[136]	Not PEF over/under a certain threshold versus asthma status
BELLIA1985[147]	Not PEF for diagnosis (prognosis of morning dip)
BERNSTEIN1993[162]	Occupational asthma

Reference	Reason for exclusion
BERRY1985[165]	Not PEF over/under a certain threshold versus asthma status
BOULET1994[204]	Not PEF over/under a certain threshold versus asthma status
BRAND1991[212]	Not PEF over/under a certain threshold versus asthma status
BRAND1997B[214]	Not PEF over/under a certain threshold versus asthma status
BRITTON1997[226]	Not PEF over/under a certain threshold versus asthma status
BROUWER2006[232]	Not PEF over/under a certain threshold versus asthma status
CHU2008[325]	Not primary study; not PEF over/under a certain threshold versus asthma status
COTE1990[365]	Occupational asthma
CURRIE2005[380]	Not PEF over/under a certain threshold versus asthma status
DESALU2009[425]	Wrong population. Reference standard – no objective test.
DICKINSON1999[436]	Not PEF versus another test for asthma (PEF included in the definition of asthma)
DOW2001[447]	Not PEF versus another test for asthma (PEF included in the definition of asthma)
ENRIGHT1997[474]	Not PEF over/under a certain threshold versus asthma status or other test
FERDOUSI1997[489]	Not PEF over/under a certain threshold versus asthma status
FERDOUSI2005[490]	Not doctor-diagnosed asthma
FIELDER1999[493]	Not PEF over/under a certain threshold versus asthma status
FRISCHER 1995[520]	Wrong population: general population, not suspected asthma.
FRISCHER1993B[519]	Not PEF over/under a certain threshold versus asthma status
GIBSON1995[558]	Case control study
GOLDSTEIN 2001[580]	PEFv calculation includes post-BD values
HANSEN1994[633]	Not PEF over/under a certain threshold versus asthma status

Reference	Reason for exclusion
HARGREAVE1982[636]	Not PEF over/under a certain threshold versus asthma status
HARGREAVE1986[635]	Not PEF over/under a certain threshold versus asthma status
HART2002[638]	Not primary study
HEDMAN1998[647]	PEF included in the definition of asthma (i.e. in reference standard not index test)
HENDERSON1989[654]	Case control study
HETZEL1980[667]	Not PEF over/under a certain threshold versus asthma status
HIGGINS 1992[669]	Wrong reference standard: Physician Dx but no objective test.
HIGGINS1989[670]	Not PEF over/under a certain threshold versus asthma status or sensitivity/specificity
HSU1997[704]	Not PEF over/under a certain threshold versus asthma status or sensitivity/specificity
JAIN1998[741]	No numerical data for sensitivity/specificity; not a primary study
JAMISON1993[747]	Case control study
JINDAL2002[770]	Not a primary study
KERCSMAR1996[840]	Not a primary study
KHOO1984[853]	Not PEF over/under a certain threshold versus asthma status
KOH2005[888]	Not PEF over/under a certain threshold versus asthma status
KOLBE1996[892]	Not PEF over/under a certain threshold versus asthma status
KUNZLI 1999[932]	Wrong population: general population, not suspected asthma.
LAPRISE1997[955]	Not PEF over/under a certain threshold versus asthma status
LARSSON1994[958]	Not PEF over/under a certain threshold versus asthma status (PEF included in diagnosis)
LARSSON1995[957]	Not PEF over/under a certain threshold versus asthma status (PEF included in diagnosis)
LAWSON2011[967]	Not PEF over/under a certain threshold versus asthma status
LEBOWITZ1997[971]	Not PEF over/under a certain threshold versus asthma status
LEWIS 2001[994]	Wrong population: general population, not suspected asthma.

Reference	Reason for exclusion
	Wrong reference standard: Physician Dx but no objective test.
LINDENSMITH2004[1007]	Not PEF over/under a certain threshold versus asthma status
LINNA1993[1014]	Not PEF over/under a certain threshold versus asthma status
MAGYAR1998[1050]	Not primary study
MATSUNAGA2008[1094]	Not PEF over/under a certain threshold versus asthma status
MICHOUD1982[1130]	Not PEF over/under a certain threshold versus asthma status
MOORE2009[1165]	Function of different monitoring devices not PEF over/under a certain threshold versus asthma status or other test
MOSCATO1993[1169]	Occupational asthma
MOSFELDTLAURSEN1993[1170]	Not PEF over/under a certain threshold versus asthma status
MUERS1984[1175]	Not PEF over/under a certain threshold versus asthma status
PAGGIARO1993[1282]	Not PEF over/under a certain threshold versus asthma status or sensitivity/specificity
PARAMESWARAN1999[1293]	Not PEF over/under a certain threshold versus asthma status
PINO1996[1351]	Not PEF variability over/under a certain threshold versus asthma status; PEF during bronchodilator test versus FEV1 during bronchodilator test – included in bronchodilator response review
PODER1987[1359]	Not PEF over/under a certain threshold versus asthma status
POGSON2009[1360]	Not PEF over/under a certain threshold versus asthma status
PRIETO1998[1391]	Not PEF over/under a certain threshold versus asthma status
PRIETO2000[1392]	Not PEF over/under a certain threshold versus asthma status
SANO2004[1494]	Not all patients had reference standard test
SEKEREL1997[1542]	Not PEF over/under a certain threshold versus asthma status
SHAKERI2012[1552]	Mixed population of patients with asthma and COPD
SHIRAHATA2005[1566]	Not PEF over/under a certain threshold versus asthma status
SIERSTED 1994[1573]	Wrong reference standard: Physician Dx but no objective test.
SIERSTED 1996[1574]	Wrong reference standard: Physician Dx

Reference	Reason for exclusion
	but no objective test. Wrong population: general population, not suspected asthma.
SINGH2012[1597]	Case control study
SLIEKER 2003A[1607]	Wrong outcome measure: PEF not PEF variability.
STEIN1997[1654]	Not PEF over/under a certain threshold versus asthma status
TAJI2013[1698]	Not PEF over/under a certain threshold versus asthma status
THIADENS 1999[1728]	Index test is BDR
TIMONEN1997[1738]	Not PEF over/under a certain threshold versus asthma status
TOKUYAMA1998[1748]	Not PEF over/under a certain threshold versus asthma status
TOUNGOUSSOVA2007[1760]	Not PEF over/under a certain threshold versus asthma status
VANSCHAYCK1996[1817]	Not PEF over/under a certain threshold versus asthma status
VARGAS2005[1824]	Not PEF over/under a certain threshold versus asthma status
VASAR1996[1826]	Not PEF over/under a certain threshold versus asthma status
VENABLES1984[1831]	Not PEF over/under a certain threshold versus asthma status
YOO2007[1936]	Not PEF over/under a certain threshold versus asthma status
YURDAKUL2005[1945]	PEF variability included as part of reference standard as well as index test
ZILMER2011[1965]	Not PEF over/under a certain threshold versus asthma status
ZUREIK1995[1970]	Not PEF over/under a certain threshold versus asthma status with a reference standard (comparing 2, 3 or 4 measurements of PEF versus 5)

K.9 Diagnosis: Skin prick tests

Table 217: Studies excluded from the clinical review

Reference	Reason for exclusion
ALENIZI2013[35]	Conference abstract – have enough fully published data already
ALMEIDA 1999[389]	Results for SPT not given thus cannot calculate sens/spec.
ANTOLIN2013[55]	Conference abstract – have

Reference	Reason for exclusion
	enough fully published data already
ANTOLINAMERIGO 2012[54]	Conference abstract – have enough fully published data already
ARDUSSO 2009[63]	Conference abstract – have enough fully published data already
ARMENTIA2007[71]	no data on SPT by/within asthma status
BARNIG 2013[113]	Correlation study – cannot calculate sens/spec.
BONINI 2010[189]	Conference abstract – have enough fully published data already
BRAND 1993[215]	Results in mixed population of asthma/COPD (no asthma subgroup analysis).
BUSINCO1988[252]	not SPT by asthma status
CAIMMI2013A[261]	Conference abstract – have enough fully published data already
COMERT2014[357]	No reference standard
CONNOLLY1981[358]	not SPT by asthma status
DEANE2005[403]	not SPT by asthma status
DELACOURT1994[411]	control group too young (<1 year)
DERVADERICS2002[424]	no data on SPT by/within asthma status
DHARMAGE1998[430]	not SPT by asthma status
DIBEK 2007[435]	All asthma pts – no comparative test group thus unable to calculate sens/spec.
ESCUDERO 1993[478]	Wrong reference standard: allergen challenge was part of the reference standard test.
FOUCARD1973[506]	longitudinal not cross-sectional data
FUIANO2013[526]	Conference abstract – have enough fully published data already
GARCIA1997[541]	patients selected for previous negative SPT
GARCIAGONZALEZ1999[542]	castor bean pollen not relevant to UK
GOETZ2007[574]	Asian ladybug not relevant to UK, no other SPT by asthma reported

Reference	Reason for exclusion
GRADMAN2006[583]	Some children had both asthma and rhinitis; table of SPT by diagnosis double counts these children so sensitivity/specificity not calculable
GRAIF 2002[584]	Wrong comparison: data in this study are given for suspected asthma pts or control pts only and are for test vs. test rather than test vs physician Dx (which is the comparison we look for in suspected asthma pts)
GUDELJ 2012[601]	Wrong reference standard: physician Dx includes the objective test
GUERRA1995[604]	Percentages given for SPT positive and negative and number with asthma but unable to calculate raw data or sensitivity/specificity etc due to rounding
HAYES2013[645]	All patients had positive SPT
HILL1994[672]	not SPT by asthma status
HUERTAS2011[711]	All pollen-allergic; no data on SPT by asthma status
IMBEAU1978[729]	not SPT by asthma status
JULIA1995[785]	Population is rhinitis and/or asthma (not suspected asthma)
KARAKAYA 2006[815]	Asthma/rhinitis pts – does not split results for asthma or rhinitis groups separately, thus cannot calc sens/spec for asthma.
KAUFMAN1984[824]	not SPT by asthma status
KIM 2002[863]	Wrong reference standard definition: Physician Dx = patient-reported in a questionnaire.
KIM2013A[858]	General population
KOUTSOUPIAS2013A[910]	Conference abstract – have enough fully published data already
KOWAL 2009[914]	Unable to calculate sens/spec as the number of +ve and –ve SPTs are bnit given for SPT with asthma.
KUMAR2011A[928]	Conference abstract – have enough fully published data already

Reference	Reason for exclusion
KUMARI 2006[931]	Wrong allergens / country for allergen: food allergies and pollen in India.
LAURENT1994[966]	SPT to diagnose winter pollinosis not asthma
LEWIS1989[991]	Case-control study including asthma and suspected asthma groups in the sensitivity/specificity analysis
LUISI 2012[1033]	All asthma pts, but unable to calculate sens/pec of SPT vs. other tests (BDR or spirometry).
MARINOVIC2013[1077]	Conference abstract – have enough fully published data already
MASULLO1996[1086]	All SPT positive
MIGUERES2011[1135]	selected for positive skin prick tests
MOSBECH 1987A[1168]	All asthma pts but wrong comparative test: bronchial, conjunctival challenge wit the same allergen as the index (SPT) test.
MURRAY1985[1184]	not SPT by asthma status
MUSKEN2002[1186]	not SPT by asthma status
NEGRINI1992[1206]	not SPT by asthma status
NIEDOSZYTKO2007[1226]	not symptomatic controls
NIEMEIJER 1992A[1228]	All asthma pts – SPT but no comparison test, thus cannot calculate sens/spec.
NOGUEIRA1994[1242]	Non-English
NOLTE 1990[1244]	Suspected asthma pts recruited, but no final Physician Dx of asthma was done and the wrong comparison tests also used.
OSTERGAARD 1990[1277]	All asthma pts: wrong comparison test - IgE or BPT with the allergens.
PALMACARLOS2005[1283]	not SPT by asthma status
PANASZEK 2007[1287]	Does not give SPT results for Dx of asthma – cannot calc sens/spec.
PANICHWATTANA2013[1288]	Conference abstract – have enough fully published data already
PAPA2001[1291]	selected for SPT positivity
PEARLMAN 2009[1308]	Correlation study and cannot calculate sens/spec for asthma

Reference	Reason for exclusion
	pts..
QUIRALTE2005[1403]	all SPT positive
RESANO1998[1437]	Intradermal not skin prick test
RODRIGUEZ2013[1455]	Not in English
ROTTOLI1989[1470]	not SPT by asthma status
SASTRE 1996[1498]	Duplicate study – already excluded
SASTRE1996[1498]	not SPT by asthma status
SCHWARTZ1995[1530]	not SPT by asthma status
SILVESTRI1996[1582]	not SPT by asthma status
SILVESTRI1997[1581]	not SPT by asthma status
SMITH2005[1612]	not SPT by asthma status
SRITIPSUKHO 2004[1649]	All asthma pts – no comparative test group thus unable to calculate sens/spec.
STAFANGER 1986[1650]	Wrong comparison test: BPT (contains the same allergens as the index SPT)
STELMACH 2002A[1655]	Results for SPT allergens divided by cockroach allergen – ve and +ve pts; cannot calc sens/spec of true asthma pts.
STOKES2000[1665]	not SPT by asthma status
TASKINEN 1997[1713]	Wrong allergen results: results for >10 moulds all pooled together. Unable to get specific results for C*ladosporium* or *Alternaria*
TAUBER 2000[1714]	Correlation study – cannot calculate sens/spec.
TOMASSEN2013[1752]	General population/no objective test
TORRESRODRIGUEZ2012[1759]	All skin prick positive
TROISE1992[1766]	not SPT by asthma status
TSCHOPP 1998[1768]	Wrong reference standard definition: Physician Dx = patient-reported in a questionnaire.
VARELA2003[1823]	SPT given for asthma group but not for control group
VENTURA2007[1835]	Some participants had both asthma and rhinitis so sensitivity/specificity not calculable
VERVLOET1999[1839]	All skin prick positive
VIEIRA 2009[1842]	Conference abstract – have enough fully published data already

Reference	Reason for exclusion
VIEIRA 2011[1843]	Wrong reference standard definition: Physician Dx = patient-reported in a questionnaire. Validation study.
WEINTRAUB 2001[1883]	Wrong definition of physician Dx: physician Dx was patient-reported via a questionnaire
WOODMANSEE 2009[1915]	Conference abstract – have enough fully published data already
YURDAKUL 2005[1945]	Case-control study including asthma and suspected asthma groups in the sensitivity/specificity analysis
ZETTERSTROM 1972[1953]	Wrong country for allergen: pollen in Sweden.

K.10 Diagnosis: IgE

Table 218: Studies excluded from the clinical review

Reference	Reason for exclusion
ABDULAMIR 2009[7]	Wrong outcomes: levels and correlations of IgE not no. of positive/negative.
ABUT 2007[14]	Wrong outcomes: correlations of IgE not no. of positive/negative.
ADLER 1985[19]	Wrong outcomes: levels of IgE not no. of positive/negative.
AGATA 1993[20]	Wrong comparisons: different IgE methods compared.
AHLSTEDT 1974[22]	Mixed population (asthma and/or allergic rhinitis), with no separate analysis for Dx of asthma.
AHMAD 2008[23]	Incorrect study design: case-control study
AKCAKAYA 2005[27]	Wrong outcomes: only gives SPT results, not IgE.
ALMQVIST 2007[37]	Wrong outcomes: predictors of subsequent development of sensitisation.
BACKER 1992[91]	Mixed population (asthma, rhinitis and dermatitis), with no separate analysis for Dx of asthma.
BARNES 2014[112]	Conference abstract
BEEH 2000[138]	Cannot calculate sens/spec as only gives numbers who were positive for each test individually.
BJORNSSON 1994[177]	Wrong outcomes: correlations of IgE not no. of positive/negative.

BRANCATO 1995[210]	Wrong outcomes: levels of IgE not no. of positive/negative.
BRAND 1993[215]	Mixed population (asthma and COPD), with no separate analysis for Dx of asthma
BRUCE 1976[235]	Wrong outcomes: levels of IgE and split by HLA antuigen groups, not no. of positive/negative.
BRYANT 1975[240]	Wrong reference standard: allergen-specific BPT.
BURROWS 1991[250]	Wrong outcomes: predictors of subsequent development of asthma.
BUTERLEVICIUTE 2013[257]	Conference abstract
CANTANI 1990[267]	Mixed population (asthma and/or rhinitis with others), with no separate analysis for Dx of asthma. Wrong outcomes: Dx of atopy, not asthma.
CANTANI 2005A[269]	Wrong outcomes: levels of IgE not no. of positive/negative.
CANTONI 2003[268]	Cannot calculate sens/spec as only gives numbers who were positive for each test individually.
CARSIN 2013[284]	Wrong outcomes: predictors of subsequent development of asthma.
CASSIMOS 2008[289]	Wrong outcomes: levels and correlations of IgE not no. of positive/negative.
CHAKRABARTI 1993[296]	Wrong outcomes: Dx of Aspergillus lung disease not asthma.
CHAO 2001[300]	Incorrect study design: case-control study.
CHEN 2014[307]	General population
CHOI 2005[317]	Wrong outcome (Dx): Dx of early or late airway reaction, not asthma Dx.
CHOI 2005A[319]	Incorrect study design: case-control study
CHOU 2002[320]	Cannot calculate sens/spec as only gives numbers who were positive for asthma only.
COCKCROFT 1979[352]	Wrong outcomes: correlations/relationships of IgE not no. of positive/negative.
COOKSON 1976[359]	Wrong outcomes: correlations of IgE not no. of positive/negative.
CRAMERI 1998[370]	Wrong outcomes:levels of IgE not no. of positive/negative.
CULLINAN 2004[379]	Wrong outcomes: not Dx of asthma.
CUSTOVIC 1996[382]	Does not mention IgE.
DECLERK 1986[393]	Wrong comparison: methods/assay development.

DELOVIN 1994[398]	Wrong comparison: sens/spec of RAST vs. mite-levels in mattress.
DOEKES 1996[442]	Wrong comparison: two different methods of IgE measurement.
DUC 1988[455]	Mixed population (asthma and/or rhinitis with others), with no separate analysis for Dx of asthma.
EWAN 1990[480]	Mixed population (asthma and/or rhinitis with others), with no separate analysis for Dx of asthma.
EYSINK 2001[481]	Wrong outcomes: predictors of subsequent development of asthma.
EYSINK 2005[482]	Cannot calculate sens/spec as only gives numbers who were positive for each test individually.
FERNANDEZ 2007[492]	Wrong reference standard: allergen-specific BPT.
FERNANDEZ 2011[491]	Wrong reference standard: allergen-specific BPT.
FLAHERTY 1980[497]	Wrong study design: case-control study. Wrong outcomes: levels of IgE not no. of positive/negative.
FREIDHOFF 1993[516]	Cannot calculate sens/spec as only gives numbers who were positive or negative for each test individually.
FRITH 2011[521]	Wrong comparison: SPT
GERGEN 2009[553]	Cannot calculate sens/spec as only gives numbers of positives for each test individually.
GODFREY 1975[570]	Wrong outcomes: levels of IgE not no. of positive/negative.
GOLDSTEIN 2005[578]	Wrong population: not asthma but allergy
HAATELA 1981[612]	Mixed population (wheeze or asthma), with no separate analysis for Dx of asthma.
HEIDEN 2010[649]	Incorrect study design: case-control study. Wrong outcomes: levels and relationships of IgE, not no. of positive/negative.
HOFFMANN 2013[677]	Wrong comparison (SPT)
HOGARTH 1973[678]	Wrong comparison: SPT
IWAMOTO 1990[736]	Incorrect study design: case-control study
JAAKKOLA 2006[737]	Incorrect study design: case-control study
JACKOLA 2004[738]	Wrong outcomes: levels and correlations of IgE not no. of positive/negative.
JANG 2007[750]	Incorrect study design: case-control

	study
KALYONCU 1995[807]	Incorrect study design: case-control study. Wrong outcomes: levels of IgE not no. of positive/negative.
KARADAG 2007[813]	Wrong outcomes: not Dx of asthma but of atopic eczema (in general population).
KARTASAMITA 1994[818]	Wrong outcomes: levels and correlations of IgE not no. of positive/negative.
KEIL 2006[832]	Review – used as a source of references.
KELSO 1991[838]	Mixed population (asthma and/or rhinitis), with no separate analysis for Dx of asthma.
KERKHOF 2003[842]	Mixed population (asthma and/or allergy symptoms), with no separate analysis for Dx of asthma.
KHADADAH 2000A[846]	Wrong comparison: SPT
KING 2004[867]	Wrong outcomes: levels of IgE and Odds, not no. of positive/negative.
KITANI 1993[869]	Does not answer the question: compares drug-induced asthma vs. non-drug induced asthma, and only gives numbers who were positive for each test individually.
KJAER 2008[873]	Wrong outcomes: results for SPT and IgE are combined.
KLINKANOVA 1995[878]	Abstract not fully published paper.
KOIVIKKO 1991[889]	Cannot calculate sens/spec.
KONDERAK 2013[897]	Conference abstract
KOROL 2006[902]	Wrong study design: case-control. Wrong outcomes: levels of IgE, not no. of positive/negative.
KOVAC 2007[911]	Wrong outcomes: asthma severity.
KURIMOTO 1978[933]	Wrong outcomes: agreement with IgE, not no. of positive/negative.
LAI 2002[950]	Cannot calculate sens/spec as only gives numbers who were positive for each test individually.
LASKE 2003[959]	Wrong outcomes: levels of IgE not no. of positive/negative.
LODRUPCARLSEN 2010A[1023]	Wrong outcomes: predictors of subsequent development of asthma.
MASUKO 2011[1085]	Wrong population: healthy people only. Wrong outcomes: levels of IgE.
MATRICARDI 1990[1090]	Mixed population (asthma and/or oculorhinitis with others), with no separate analysis for Dx of asthma.
MATRICARDI 2009[1088]	Wrong outcomes: levels of IgE over time, not no. of positive/negative.

MATSUI 2010[1091]	Wrong outcomes: levels of IgE not no. of positive/negative.
MOGI 1977[1156]	Incorrect study design: case-control study. Wrong outcomes: levels of IgE not no. of positive/negative.
MOGI 1977A[1157]	Wrong outcomes: levels and correlations of IgE not no. of positive/negative.
MOUTHUY 2011[1173]	Wrong outcomes: levels of IgE not no. of positive/negative.
MOVERARE 2002[1174]	Mixed population (asthma and/or rhinoconjunctivitis), with no separate analysis for Dx of asthma.
MUSTONEN 2013[1188]	Wrong outcomes: predictors of asthma over time linked to CRP.levels of IgE not no. of positive/negative.
MYGIND 1978[1190]	Wrong outcomes: levels of IgE not no. of positive/negative.
NAVRATIL 2009[1205]	Wrong outcomes: levels and relationships of IgE, not no. of positive/negative.
NIELSEN 1992[1227]	Results for all allergens pooled together.
NIGGEMAN 2008[1231]	Wrong outcomes: Dx of allergy made with symptoms and IgE,not Dx of asthma.
NOLLES 2001[1243]	Wrong outcomes: not Dx of asthma.
NUSSLEIN 1987[1250]	Wrong comparison: old RAST vs. new RAST
OKUDAIRA 1983[1265]	Cannot calculate sens/spec as only gives numbers for each test individually.
ORYSZCZYN 2009[1273]	Not IgE versus SPT status; cannot calculate sensitivity etc of test.
OSTERBALLE 1979[1276]	Cannot calculate sens/spec as only shows data as graphs.
PANZANI 1993[1290]	Not physician diagnosed asthma and no objective tests.
PARK 1997[1299]	Wrong outcomes: not Dx of asthma.
PASTORELLO 1995[1304]	Wrong outcomes; Dx of symptomatic and non-symptomatic allergy, not asthma.
PEAT 1996[1311]	Wrong outcomes: levels of IgE not no. of positive/negative.
PECOUD 1982[1314]	Wrong comparison: newer RAST test vs. older RAST test.
PEKKARINEN 2007[1318]	Cannot calculate sens/spec as only gives numbers who were positive for each test individually.
PELIKAN 1982[1319]	Results for all allergens pooled together.
PEPYS 1975[1320]	Mixed population (asthma and/or allergic rhinitis), with no separate

	analysis for Dx of asthma.
PEREIRA 2005[1321]	Mixed population (asthma and/or allergic rhinitis), with no separate analysis for Dx of asthma.
PERRIN 1983[1324]	Wrong outcomes: levels of IgE not no. of positive/negative.
PERZANOWSKI 1998[1330]	Report of data from several other studies.
PLASCHKE 1996[1355]	Wrong outcomes: not Dx of asthma but of atopy (in general population).
PLEBANI 1995[1356]	Not asthma versus no asthma (mixed population of asthma and rhinitis patients)
PRICE 1989[1388]	Wrong outcomes: % agreement of SPT and RAST, not no. of positive/negative.
PRICHARD 1985[1389]	Occupational asthma.
RAHERISON 2004[1408]	Wrong outcomes: levels of IgE not no. of positive/negative.
REIJULA 2003[1431]	Mixed population (asthma with others), with no separate analysis for Dx of asthma. Incorrect study design: case-control study.
ROGERS 2002[1457]	Not asthma versus no asthma (not Dx of asthma); no reference standard or other test for allergy
ROSARIO 1997[1466]	Wrong outcomes: levels and correlations of IgE not no. of positive/negative.
RUDZKI 1990[1474]	Wrong population: atopic dermatitis pts.
RYDJORD 2008[1479]	Wrong outcomes: not used for Dx of asthma.
SANTOSO 1998[1496]	Wrong comparison: SPT
SCHOEFER 2008[1522]	Wrong outcomes: levels of IgE not no. of positive/negative.
SCORDAMAGLIA 1992[1533]	Mixed population (asthma, rhinitis and conjunctivitis), with no separate analysis for Dx of asthma.
SELASSIE 2000[1543]	Incorrect study design: case-control study
SHARMA 2006A[1556]	Incorrect study design: case-control study.
SHERRILLI 1999[1560]	Wrong outcomes: wheezing, not Dx of asthma.
SHIBASAKI 1997[1561]	Incorrect study design: case-control study
SIMONI 2001[1588]	Wrong test: PRIST test (modified RAST test) – not commonly used in current practice.
SIMPSON 2005[1589]	Wrong outcomes: Dx of wheeze not asthma.

SIROUX 2003[1599]	Correlation study in people with asthma
STAFANGER 1986[1650]	Cannot calculate sens/spec as only gives data in graphs.
STEVENS 1983[1660]	Mixed population (asthma and/or rhinitis), with no separate analysis for Dx of asthma.
STEVENS 2011[1659]	Incorrect study design: case-control study
SUBIRA 1976[1677]	Wrong outcomes: levels and correlations of IgE not no. of positive/negative.
SUMAN 2005[1679]	Incorrect study design: case-control study. Wrong test: for indian-specific pollen.
SUNYER 1996[1682]	Cannot calculate sens/spec as only gives numbers who were positive for each test individually.
SUNYER 2004[313]	Not asthma versus no asthma (not Dx of asthma); no reference standard or other test for allergy
TAMURA 1991[1704]	Wrong outcomes: predicted true positives and negatives, not actual numbers.
TANG 1989[1707]	Wrong comparison: SPT
TANG 2010[1706]	Wrong outcomes: levels of IgE not no. of positive/negative.
TERZIOGLU 1998[1725]	IgE vs. SPT (measures of the same thing); no comparison with Physician Dx.
TOMASSEN 2013[1752]	General population / wrong comparison (SPT).
TORRENT 2006[1756]	Wrong outcomes: risk of sensitisation, not Dx of asthma.
TU 2013[1776]	Conference abstract
VAGIC 2008[1791]	Incorrect study design: case-control study. Wrong outcomes: levels of IgE not no. of positive/negative.
VALENCIA 1993[1793]	Mixed population (asthma or rhinitis), with no separate analysis for Dx of asthma.
VANTO 1982[1822]	Wrong reference standard: allergen-specific BPT.
VIANDER 1983[1841]	Wrong comparison: conjunctival provocation test.
VOOREN 1983[1856]	Wrong reference standard: allergen-specific BPT.
WAKAMORI 2009[1861]	Wrong population: dermatitis not asthma.
WANG 1992[1871]	Wrong test: MAST test – not commonly used in current practice. RAST test also used in study but results not reported.

WANG 2009[1870]	Wrong outcomes: levels of IgE and predictors of mortality.
WEDNER 1987[1879]	Wrong allergen: rare plant
WEINMAYR 2007[1882]	Wrong outcomes: not used for Dx of asthma.
WICKMAN 2005[1892]	Mixed population (asthma and/or allergic rhinitis), with no separate analysis for Dx of asthma.
WITTEMAN 1996[1905]	Wrong outcomes: levels of IgE not no. of positive/negative.
WOODMANSEE 2009[1915]	Abstract only (conference abstract, not a full paper)
YANG 2010[1928]	Abstract only (conference abstract, not a full paper)
YAZICIOGLU 1994[1932]	Incorrect study design: case-control study. Results for all allergens pooled together.
ZIMMERMAN 1988A[1966]	Mixed population (asthma and/or rhinitis and others), with no separate analysis for Dx of asthma.

K.11 Diagnosis: FeNO

Table 219: Studies excluded from the clinical review

Reference	Reason for exclusion
ANSARIN2001[52]	Not treatment naïve (>50% on CS treatment)
ANTUS2010[56]	Not treatment naïve (>50% on CS treatment)
ARTLICH1996[75]	N<50 for case-control study
AVITAL2001[84]	Reference standard objective test not widely used
BACKER 2014[92]	Reference standard does not match protocol – sn/sp of FeNO to predict positive mannitol in suspected asthma (not physician diagnosis and objective test)
BAKKEHEIM2011[95]	Not treatment naïve (>50% on CS treatment)
BALINOTTI2013[98]	No objective test for asthma, only Asthma Predictive Index
BARALDI2003[105]	Case-control study for FeNO levels but <50 people
BARALDI2003A[102]	Not treatment naïve (>50% on CS treatment)
BARALDI2005[104]	N<50 for case-control study
BARALDI2006[103]	Case-control study for FeNO levels but <50 people
BARRETO2001[115]	Not treatment naïve (unclear % of

Reference	Reason for exclusion
	patients on CS treatment)
BARRETO2006[116]	N<50 for case-control study
BEG2009[141]	Index test does not match protocol – flow rate of 200ml/s
BEIGELMAN2008[142]	Not treatment naïve and no objective test
BERKMAN2005[160]	Index test does not match protocol – flow rate of 250ml/s
BERNSTEIN2009[163]	Not treatment naïve (no restrictions on treatment)
BERRY2005A[164]	Not treatment naïve (>50% on CS treatment)
BEVER2003[167]	Non-English
BOBOLEA2012[182]	Not full paper (letter)
BOMMARITO2008[185]	Not treatment naïve; no objective test
BRINDICCI2007[225]	N<50 for case-control study
BRODLIE2010[227]	Review not primary study
BRUSSEE2005[237]	Population does not match protocol – general population.
BYRNES1997[259]	Not treatment naïve (>50% on CS treatment)
CARRARO2005[280]	N<50 for case-control study
CARRARO2007A[282]	Not treatment naïve (>50% on CS treatment)
CARRARO2010[281]	N<50 for case-control study
CASTRORODRIGUEZ2013[291]	All people with asthma for FeNO levels but <50 people
CHEROTKORNOBIS2011[308]	Case-control study for FeNO levels but <50 people
CHO2013[314]	Index test does not match protocol – incorrect flow rate
CHOW2009[321]	Results split into obese vs. non-obese pts; if use the non-obese people with asthma it means N<50 for case-control study. Otherwise meets all inclusion criteria.
CIPRANDI2010[333]	Reference standard does not match protocol – unclear if objective test used
COLONSEMIDEY2000[356]	All people with asthma for FeNO levels but <50 people
CORRADI2001[361]	N<50 for case-control study (if exclude the subgroup on CS Tx)
CRANE2012[371]	Not treatment naïve; no objective test
DEBLEY2010[405]	Asthma only pts, but N<50.
DEBOT2013[392]	No objective test
DECIMO2011[406]	Meets all inclusion criteria, but does not report the FeNO levels.

Reference	Reason for exclusion
DEDIEGO2005[394]	FeNO levels but <50 people; not sensitivity/ specificity vs. other test
DEGOUW2001[395]	N<50 for case-control study
DEGROOT2012[396]	Not treatment naïve (all on CS treatment)
DELEN2000[413]	Not treatment naïve (unclear % of patients on CS treatment)
DELGIUDICE2004[409]	All people with asthma for FeNO levels but <50 people
DEMEER2005[401]	No relevant outcomes – cannot calculate sn/sp of FeNO for Dx of asthma
DOTSCH1996[446]	Unclear physician Dx.
DRESSEL2008[448]	Method of asthma Dx not reported.
DRESSEL2010[449]	Unclear physician Dx.
EKROOS2009[467]	Index test does not match protocol – flow rate of 80-150ml/s
ELHALAWANI2003[468]	Suspected EIB and exercise challenge test.
ELLIOTT 2013[471]	Population does not match protocol – children less than 1 year old
FABBRI2003[483]	Case-control study for FeNO levels but <50 people
FITZPATRICK2006[496]	Severe asthma and moderate asthma. If exclude the sever asthma subgroup then N<50 for case-control study.
FORMANEK2002[504]	Index test does not match protocol – nitrite levels not FeNO
FORTUNA2007[505]	Reference standard objective test does not match protocol – methacholine challenge test cut-off at 16mg/ml
FOWLER2009[509]	Not treatment naïve (>50% on CS treatment)
FRANK1998[513]	Not treatment naïve (unclear % of patients on CS treatment)
FRANKLIN2003[514]	Population does not match protocol – general population, asymptomatic children
FRANKLIN2004[515]	Population does not match protocol – general population
FUJIMURA2008[528]	FeNO levels but <50 patients
GABRIELE2005[530]	All people with asthma for FeNO levels but <50 people
GADE2009[531]	Asthma only pts but N<50.
GAGLIARDO2009[532]	Not treatment naïve (>50% on CS treatment)
GEVORGYAN2013[554]	Review not primary study
GRONKE2002[594]	Population does not match protocol – all

Reference	Reason for exclusion
	atopic and comparing FeNO levels in groups with different durations of asthma
GRZELEWSKI 2014[600]	Study does not report results in such a way that it is possible to calculate sensitivity and specificity.
HAHN 2007	Sn/sp of FeNO for predicting response to ICS treatment, not asthma
HENRIKSEN2001[659]	Not treatment naïve (unclear % of patients on CS treatment)
HENRIKSEN2002[661]	No relevant outcomes – cannot calculate sn/sp of FeNO for Dx of asthma
HENRIKSEN2003[660]	Not treatment naïve (unclear % of patients on CS treatment)
HERVAS2008[665]	Not treatment naïve (unclear % of patients on CS treatment)
HOGMAN2001[680]	Not treatment naïve (>50% on CS treatment)
HOGMAN2002[679]	Not treatment naïve (>50% on CS treatment)
HOLGUIN2011[681]	Not treatment naïve (>50% on CS treatment)
HORVATH2004[701]	Physician Dx with no objective tests (just does SPT).
HOVI2010[703]	Non-English
HSU2013[705]	Sn/sp of FeNO for predicting response to ICS treatment, not asthma
HUSZAR2002[718]	Index test does not match protocol – flow rate of 5-6L/min
ISHIZUKA2011[733]	No objective test
JATAKANON1998A[762]	All asthma pts but N<50
JENTZSCH2006[767]	Not treatment naïve (>50% on CS treatment)
JERZYNSKA 2014[768]	Study does not report results in such a way that it is possible to calculate sensitivity and specificity.
KANAZAWA2004[809]	Case-control study. Phys Dx with objective test but wrong cut-off for objective test (BDR >20% - should be 12%)
KATSOULIS2013[820]	Reference standard does not match protocol – sn/sp of FeNO to predict positive methacholine challenge test not physician diagnosis of asthma with objective test.
KEEN2011[831]	Not treatment naïve (>50% on CS treatment)
KHARITONOV2003[850]	Unclear physician Dx.

Reference	Reason for exclusion
KIELBASA2008[856]	Not treatment naïve (>50% on CS treatment)
KIM2013[864]	Wrong-cut off for the MCT objective test as part of Phys Dx. MCT <16mg/ml or FEV1 12% (doesn't give the % Dx by MCT or FEV1).
KLEIS2007[876]	Wrong-cut off for the MCT objective test as part of Phys Dx. MCT <16mg/ml – should be 8mg/ml.
KO2009[884]	Not treatment naïve (>50% on CS treatment)
KOMAKULA2007[895]	Not treatment naïve (>50% on CS treatment)
KONDO2003[898]	FeNO levels but <50 people
KOSKELA2008[904]	Not treatment naïve (>50% on CS treatment)
KOVESI2008[913]	Not treatment naïve (unclear % on CS treatment)
KOVESI2009[912]	No objective test
LAGRUTTA2003[942]	Not treatment naïve (>50% on CS treatment)
LANGLEY2003[954]	Not treatment naïve (>50% on CS treatment)
LARA2008[956]	Not treatment naïve (>50% on CS treatment)
LEHTIMAKI2002[977]	FeNO levels measured but not reported in paper (only alveolar NO concentration and bronchial NO flux)
LEONDELABARRA2011[981]	Cannot calculate sn/sp
LEUPPI2002[988]	Population does not match protocol – FeNO levels in patients with atopy, not asthma
LI2006[996]	All people with asthma for FeNO levels but <50 people
LI2006A[997]	Not treatment naïve (>50% on CS treatment)
LIM2000A[1005]	Not treatment naïve (>50% on CS treatment)
LINN2009B[1011]	Population does not match protocol – general population
LUDVIKSDOTTIR2012[1032]	Review not primary study
MACLEOD2009[1043]	Not treatment naïve (>50% on CS treatment)
MALBYSCHOOS2012[1057]	All on CS Tx.
MALINOVSCHI2009[1060]	No objective test
MALINOVSCHI2012[1059]	Reference standard does not match protocol – not all patients had objective test (response to treatment only)

Reference	Reason for exclusion
MALMBERG2003[1064]	Sens/spec is calculated for the wrong population: suspected asthma vs. healthy controls.
MALMBERG2009[1065]	Comparator test does not match protocol – outdoor running test with non-standard cut-off
MANSO2011[1074]	Only reports FeNO levels but is not a case-control study or case-series. Pts are suspected asthma.
MARTINS2008[1083]	Population does not match protocol – FeNO levels in symptomatic patients, not asthma
MATSUNAGA2011[1093]	Unclear cut-off for objective test part of the Phys Dx.
MCELDOWNEY2008[1104]	FeNO levels but <50 people
MENZIES2007A[1122]	Not treatment naïve (>50% on CS treatment)
MITSUFUJI2001[1153]	FeNO levels after bronchoprovocation
MONTUSCHI2010[1163]	Unclear cut-offs for objective tests as part of the Phys Dx.
MUSK2011[1185]	Not asthma vs. no asthma
NADIF2010[1192]	Reference standard does not match protocol – no objective test
NARANG2002[1198]	Not treatment naïve (>50% on CS treatment)
NELSON1997[1209]	Not treatment naïve (>50% on CS treatment)
NICKELS2014[1219]	Conference abstract
NICKELS2014A[1220]	Conference abstract
NICOLAOU2006[1224]	Population does not match protocol – FeNO levels in general population and patients with wheeze
NOGAMI2003[1241]	No relevant outcomes – correlation of FeNO and FEV1
NORDVALL2005[1246]	Population does not match protocol – general population
OH2008[1261]	Population does not match protocol – only chronic cough and unclear treatment
OHKURA2009[1263]	Not treatment naïve (>50% on CS treatment)
OHKURA2013[1262]	Conference abstract
OJOO2005[1264]	Case-control study for FeNO levels but <50 people
OLIN2006[1268]	Population does not match protocol – general population
ONUR2011[1269]	FeNO levels but <50 people
OZAREKHANC2012[1280]	Non-English

Reference	Reason for exclusion
PARAMESWARAN2001[1292]	Case-control study for FeNO levels but <50 people
PAREDI2002[1296]	Case-control study for FeNO levels but <50 people
PAREDI2005[1297]	People with asthma only for FeNO levels but <50 people
PEDROSA2010[1316]	Reference standard objective test does not match protocol – methacholine challenge test cut-off at 16mg/ml
PEIRSMAN 2013[1317]	Study included in FeNO monitoring review
PERZANOWSKI2010[1331]	No objective test (only questionnaire report of wheeze)
PERZANOWSKI2010A[1329]	Population does not match protocol – general population
PETSKY 2010[1336]	Abstract
PETSKY 2014[1340]	Study included in FeNO monitoring review
PIACENTINI1999[1343]	People with asthma only for FeNO levels but <50 people
PIACENTINI2000[1342]	Not treatment naïve (>50% on CS treatment)
PRADO2011[1380]	Non-English
PRASAD2006[1381]	Population does not match protocol – general population
PRIETO2009[1393]	Not treatment naïve (>50% on CS treatment). Reference standard does not match protocol - ICS responsiveness.
PROFITA2010[1394]	Not treatment naïve (>50% on CS treatment)
RADULOVIC2010[1407]	FeNO levels but <50 people
RAMIREZ2010[1411]	FeNO versus C-reactive protein (not in protocol)
RAMSER2008[1413]	Sn/sp of FeNO to predict BHR or positive exercise challenge test.
RATNAWATI2006[1422]	Not treatment naïve (>50% on CS treatment)
REID2003[1430]	N<50 pts who are ICS naiive, for a study which can only calculate FeNO levels.
RICCIONI2012[1440]	Not treatment naïve (unclear % on CS treatment)
ROBINSON2012A[1452]	Population does not match protocol – general population
ROBROEKS2007[1453]	Not treatment naïve (>50% on CS treatment)
ROLLA2007[1458]	Not asthma vs. non-asthma
ROSA2011[1465]	No objective test (only questionnaire report of wheeze)

Reference	Reason for exclusion
ROSIAS2004[1467]	Not treatment naïve (>50% on CS treatment)
ROUHOS2008[1472]	Not asthma
SACHSOLSEN2010[1482]	Population does not match protocol – general population
SAITO2004[1484]	Population does not match protocol – FeNO levels in patients with and without wheeze, no Dx of asthma
SAKAI2010[1485]	Reference standard does not match protocol – no objective test
SALOME1999[1489]	Population does not match protocol – general population
SANDRINI2010[1492]	Review not primary study
SARAIVA2009[1497]	FeNO levels but <50 people; not treatment naive
SATOUCHI1996[1500]	Case-control study for FeNO levels but <50 people
SCHLEICH2012[1514]	Reference standard objective test does not match protocol - methacholine challenge test cut-off at 16mg/ml
SCHNEIDER2009[1521]	Wrong reference standard: Physician Dx with objective test, but objective test uses the wrong cut-off: methacholine at 16ug/ml (should be 8ug/ml).
SCHNEIDER2013[1520]	Wrong reference standard: Physician Dx with objective test, but objective test uses the wrong cut-off: methacholine at 16ug/ml (should be 8ug/ml).
SCHNEIDER2014[1518]	Wrong reference standard: no objective test
SCHULZE2013[1527]	Reference standard does not match protocol – no objective test
SCOLLO2000[1532]	All people with asthma for FeNO levels but <50 people
SCOTT2010[1534]	Population does not match protocol – general population
SEE2013[1539]	Population does not match protocol – general population
SETHI2010[1546]	All people with asthma for FeNO levels but <50 people
SHIN2006[1565]	Case-control study for FeNO levels but <50 people
SHORT2011[1570]	Not treatment naïve (>50% on CS treatment)
SILKOFF2000[1575]	FeNO levels but < 50 people
SILVESTRI2000[1584]	Index test does not match protocol – incorrect flow rate
SILVESTRI2001[1585]	Index test does not match protocol –

Reference	Reason for exclusion
	incorrect flow rate
SILVESTRI2003[1586]	Population does not match protocol – FeNO levels in people with atopic and non-atopic asthma
SILVESTRI2006[1580]	Case-control study for FeNO levels but <50 people
SIMON2010[1587]	No relevant outcomes – correlation analysis
SIMPSON2008[1591]	Review not primary study
SINGH2007[1596]	Treatment study; not FeNO for diagnosis or levels in asthma/non-asthma
SIPPEL2000[1598]	No relevant outcomes – correlation analysis
SMITH2004[1613]	Reference standard objective test does not match protocol - hypertonic saline challenge test
SMITH2005[1612]	Reference standard objective test does not match protocol - ICS response only used for Dx in a proportion of patients.
SONNAPPA2010[1622]	Not treatment naïve (>50% on CS treatment)
SONNAPPA2011[1621]	Population does not match protocol – FeNO levels in general population and patients with wheeze
SORDILLO2011[1626]	Population does not match protocol – general population
SPALLAROSSA2003[1636]	Wrong phys Dx – does not mention objective test.
SPITALE2012[1642]	Review not primary study
STRUNK2003[1675]	No relevant outcomes – correlation analysis
SUTHERLAND2007[1685]	Not treatment naïve; no objective test
SVERRILD2009[1689]	Population does not match protocol – general population
SVERRILD2010[1688]	Population does not match protocol – general population
TAMASI2009[1703]	Population does not match protocol – pregnancy
TERADA2001[1721]	All people with asthma for FeNO levels but <50 people
THOMAS2005[1731]	Population does not match protocol – general population
TILEMANN2011[1737]	Wrong reference standard: Physician Dx with objective test, but objective test uses the wrong cut-off: methacholine at 16ug/ml (should be 8ug/ml).
TOMASIAKLOZOWSKA2012[1751]	Case-control study for FeNO levels but

Reference	Reason for exclusion
	<50 people (excluding those on CS treatment)
TRAVERS2007[1764]	Population does not match protocol – general population
TSUJINO2000[1771]	Unclear / insufficient Dx criteria. National heart and lung institute criteria.
TUFVESSON2007[1778]	Case-control (rhinitis vs healthy controls: 26 of the rhinitis patients also had asthma but with the n=12 healthy controls this only makes n=38
TURKTAS2003[1782]	All people with asthma for FeNO levels but <50 people
UASUF1999[1788]	Reference standard does not match protocol – no objective test
VANAMSTERDAM2003[1797]	Population does not match protocol – general population
VANASCH2008[1798]	Population does not match protocol – general population
VANDERVALK2012[1808]	Population does not match protocol – general population
VANDERVALK2012A[1807]	No relevant outcomes – FeNO for monitoring
VERLEDEN1999[1837]	Population does not match protocol – smokers and non-smokers
VIEIRA2011[1843]	Population does not match protocol – general population
VISSER2000[1847]	Case-control study for FeNO levels but <50 people (excluding those on CS treatment)
VOORENDVAN2013[1857]	Conference abstract
WANG2012[1872]	Reference standard does not match protocol – not all patients had objective test
WARKE2002[1875]	No relevant outcomes – sn/sp is not for Dx of asthma
WELSH2007[1884]	Population does not match protocol – general population
WILLIAMSON2010[1900]	Not treatment naïve (>50% of asthma patients on CS treatment)
XU2011[1925]	No objective test
YAO2011[1929]	Population does not match protocol – general population
YAVUZ2012[1931]	No relevant outcomes – FeNO for monitoring
YOON2012[1938]	Not treatment naïve; not FeNO levels in asthma vs. non-asthma or diagnostic accuracy
ZETTERQUIST2008[1952]	Case-control study for FeNO levels but

Reference	Reason for exclusion
	<50 people
ZHAO2013[1954]	No objective test
ZIETKOWSKI2007[1963]	Case-control study for FeNO levels but <50 people
ZIETKOWSKI2008[1959]	Case-control study for FeNO levels but <50 people
ZIETKOWSKI2008A[1958]	Case-control study for FeNO levels but <50 people
ZIETKOWSKI2008B[1961]	Case-control study for FeNO levels but <50 people
ZIETKOWSKI2009[1964]	Case-control study for FeNO levels but <50 people
ZIETKOWSKI2010[1960]	Case-control study for FeNO levels but <50 people
ZIETKOWSKI2010B[1962]	Exclude: correlations not sensitivity/ specificity for FeNO; <50 treatment naïve patients + healthy controls

K.12 Diagnosis: Eosinophils

Table 220: Studies excluded from the clinical review

Reference	Reason for exclusion
ADJAMI 2011[18]	Conference abstract. Wrong outcomes: levels and correlations of eosinophils, not no. of positive/negative
ALVAREZPUEBLA 2003[40]	Wrong outcomes: levels and correlations of eosinophils, not no. of positive/negative
ATTAPATTU 1991[78]	General population. Wrong comparative test: blood eosinophils vs. SPT.
BARNES 1999[111]	Combinations of tests. Does not report eosinophil counts.
BJORNSSON 1994[177]	Incorrect population
BOUZIGON 2012[206]	Wrong outcomes: levels and correlations of eosinophils, not no. of positive/negative
BRAND 1993[215]	Not addressing specified population: mixed population (no asthma subgroup analysis)
BURNETT 2011[247]	Conference abstract. Wrong outcomes: levels and correlations of eosinophils, not no. of positive/negative.
BURROWS 1991[250]	Not addressing specified outcomes: predictors of

Reference	Reason for exclusion
	future disease of asthma
CRATER 1999[372]	NOT addressing specified outcomes
DIFRANCO 2003[431]	Not addressing review question: sputum eosinophil not blood; eosinophil blood levels given at baseline but N<50.
DILORENZO 2007[432]	Incorrect study design
FRANKLIN 2003[514]	Wrong outcomes: levels and correlations of eosinophils, not no. of positive/negative.
FRETTE 1991[517]	Wrong outcomes: levels and correlations of eosinophils, not no. of positive/negative
FUJIMURA 2005[527]	Predictors of future asthma development and eosinophil levels, but N<50.
HALLDEN 1999[622]	Case-control study which reports levels of eosinophils, but N<50.
HASTIE 2013[640]	Incorrect population
HYVARINEN 2010[720]	Predictors of future asthma development
IMAI 1999[728]	Case-control study which reports levels of eosinophils, but N<50.
JANG 2003[751]	Case control: but N<50 and does not report eosinophil counts at baseline, only correlations.
JUNG 2011[788]	NOT addressing review question: excluded asthma patients
KARTASAMITA 1994[818]	Not addressing specified outcomes
KOWAL 2009[914]	Not addressing specified outcomes/population
KUEHR 1994[923]	Mixed population of asthma and non-asthma but data not separated.
LECKIE 2000[972]	Wrong study: looks at effects of treatment
LIANG 2012[1000]	Not addressing review question
LIM 2010[1003]	Conference abstract. Wrong outcomes: levels and correlations of eosinophils, not no. of positive/negative.

Reference	Reason for exclusion
MAGNAN 1998[1049]	Not addressing review question. Wrong outcomes: levels and correlations of eosinophils, not no. of positive/negative.
MAHMOUD 2011[1053]	Incorrect study design
MAHMOUD 2013[1052]	Meeting abstract
MALINOVSCHI 2013[1061]	Incorrect population & reference standard
MATSUNAGA 2011[1093]	Incorrect study design. Not addressing specified outcomes
MATSUNAGA 2012[1092]	NOT addressing specified outcomes
MEYER 2014[1128]	Incorrect population
MOHAMMADIEN 2009[1158]	Wrong study/Incorrect study design: case-control study and relationships + levels
NOGAMI 2003[1241]	Not addressing specified outcomes: values not given
PALMER 2001[1285]	Not addressing clinical/review question
PARK 2013[1301]	Conference abstract
POHUNEK 2005[1361]	Wrong outcomes: predictors of subsequent development of asthma.
POSTMA 1995[1370]	Incorrect population
PRONK 2001[1395]	Case control study, but does not report levels of blood eosinophils.
RAZI 2010[1424]	Wrong outcomes: eosinophil count as predictor of response to treatment
ROQUET 1996[1464]	Levels: hyperactive versus hyperactive patients; N,50.
SOUMA 2011[1633]	Conference abstract. Wrong outcomes: associations of eosinophil levels.
SPALLAROSSA 1995[1635]	Case-control study which reports levels of eosinophils, but N<50.
SPECTOR 2012[1637]	Case-control study which reports levels of eosinophils, but N<50.
TSYBULKINA 2012[1773]	Conference abstract. Wrong outcomes: levels and correlations of eosinophils,

Reference	Reason for exclusion
	not no. of positive/negative.
ULRIK 2005[1789]	General population. Does not give +ve and –ve for eosinophils or eosinophil levels.
VOLBEDA 2013[1850]	Not disease but markers of control (i.e. monitoring)
YURDAKUL 2005[1945]	Incorrect study design
ZEDAN 2010[1950]	Incorrect study design

K.13 Diagnosis: Histamine and methacholine challenge tests

Table 221: Studies excluded from the clinical review

Reference	Reason for exclusion
ALBERTS 1994[32]	Index test and reference standard do not match protocol – sn/sp of FEF25-75% in predicting positive methacholine test
ALBORNOZ 1995[33]	All people with confirmed asthma and no comparator test
ALVAREZPUEBLA 2003[40]	Reference standard does not match protocol (Dx based on symptoms without objective test)
ANDERSON 2010A[46]	Conference abstract
ANDERSON 2011[47]	Review article
ANDREGNETTE 2011[49]	Conference abstract
ANTOLINAMERIGO 2012[54]	Conference abstract
ANTOLINAMERIGO 2013[55]	Conference abstract
AVITAL 1995[82]	Population does not match protocol – mean age < 5years
AVITAL 1995A[83]	Comparator tests do not match protocol (methacholine vs AMP and exercise) and sn/sp of methacholine not compared to reference standard of physician Dx with objective test (American Thoracic Soc diagnostic criteria for asthma)
BACKER 1991[88]	Reference standard does not match protocol – questionnaire based on symptoms and physician Dx without report of objective test
BACKER 1992[91]	No relevant outcomes and does not match review question - relationship between bronchial responsiveness and IgE
BACKER 1992B[90]	Index test does not match protocol (sn and sp of physician Dx and symptoms in relation to exercise challenge)
BACKER 1995[87]	Population does not match protocol - prevelence of positive HCT in general

Reference	Reason for exclusion
	population and correlation with asthma and atopy
BACKER 2014[92]	Index test and reference standard do not match protocol – sn/sp of FeNO to predict positive mannitol in suspected asthma (not physician diagnosis and objective test)
BAILLY 2011[94]	No relevant outcomes and does not match review question (different methods of measuring methacholine response, Pc20 used as part of reference standard for Dx)
BALLWEG 2012[100]	Review article
BARBEN 2011[107]	Index test does not match protocol – mannitol and exercise challenge test
BASIR 1995[124]	Index test does not match protocol – methacholine challenge test. No reference standard of physician diagnosis with objective test
BENNETT 1987[153]	No relevant outcomes and does not match review question (different methods of measuring methacholine and histamine response; all people with confirmed asthma and comparator does not match protocol)
BERKMAN 2005[160]	Reference standard does not match protocol – physician Dx without objective test in a proportion of patients and no data on the percentage of patients who were Dx with an objective test.
BEYDON 2008[168]	No relevant outcomes and does not match review question – correlation between BDR and methacholine response
BIBI 1991[172]	Reference standard does not match protocol – physician Dx without objective test. Cannot compare index test vs comparator test as people with suspected asthma and no suitable reference standard
BIRNBAUM 2007[175]	Review article
BONAVIA 1996[186]	Comparator tests and reference standard do not match protocol (asthma group defined by symptom score not physician Dx)
BOONSAWAT 1992[191]	Reference standard does not match protocol (physician Dx without objective test)
BOUAZIZ 1996[200]	Comparing different methods of measuring methacholine test (all patients with asthma and no comparator test)
BRAND 1993[215]	Index test does not match protocol – no challenge test performed
BRUSCHI 1989[236]	Population does not match protocol - general population not suspected asthma
BUSSE 2005[255]	Review / report from workshop

Reference	Reason for exclusion
CARLSEN 1998[275]	case-control study
CARLSTEN 2011[277]	Reference standard does not match protocol – Dx was clinical decision made by the paediatric allergist based on symptoms of wheeze and cough, use of medications and physical findings
CHATHAM 1982[303]	Sn/sp of histamine and methacholine vs exercise in people with asthma and controls (does not match this protocol comparator). No reference standard of physician Dx with objective test.
CHOI 2003[316]	Index test does not match protocol (incorrect cut-off for positive test)
CHOI 2007A[318]	Population does not match protocol (all patients had positive methacholine challenge test)
CHUNG 2010[326]	Conference abstract – sn/sp of mannitol and methacholine but reference standard not mentioned
CIPRANDI 2010[333]	No relevant outcomes and does not match review question – correlation between FeNO and methacholine PC20 and sn/sp of FeNO to predict positive methacholine test
CIPRANDI 2011[331]	Population does not match protocol – all Dx with allergic rhinitis and excluded if a history of asthma or referred with asthma symptoms
CIRILLO 2009[336]	Population does not match protocol – all Dx with allergic rhinitis and excluded if a history of asthma or referred with asthma symptoms
COCKCROFT 1979[352]	No relevant outcomes and does not match review question (correlation between allergen PC20 and histamine PC20 in people with confirmed asthma)
COCKCROFT 1992[351]	Reference standard does not match protocol – Dx based on questionnaire (previous doctor diagnosis or wheeze symptoms)
COCKCROFT 2005[350]	No relevant outcomes and does not match review question (correlation between allergen, histamine and methacholine PC20 in people with confirmed asthma)
COCKCROFT 2009[353]	Review article
COCKCROFT 2010[354]	Review article
CORDEIRO 2011[360]	Index test and reference standard do not match protocol – histamine test used as part of reference standard to Dx (index test = FeNO)
DEHAUT 1983[407]	No relevant outcomes and does not match

Reference	Reason for exclusion
	review question (different methods of measuring histamine response)
DELGIUDICE 2004[409]	No relevant outcomes and does not match review question – correlation between FeNO and PC20 (all patients with asthma but Dx made by physician with no objective test)
DEN OTTER 1997[417]	Reference standard for asthma diagnosis included methacholine/histamine challenge test
DI LORENZO 2007[432]	Case control type study with 3 groups (asthma Dx by symptoms and objective test; gastro-oesophageal reflux group with asthma symptoms; healthy controls) – study gives sn/sp values for MCT but this is based on 52% of patients having asthma (includes asymptomatic healthy control group)
DREWEK 2009[450]	Index test does not match protocol (sn and sp of FEF25-75 to measure methacholine response; diagnosis of asthma based on symptoms during challenge test)
DURAND 2011[454]	Conference abstract – reference standard not mentioned
DURZO 2012[384]	Conference abstract
FORASTIERE 1991[502]	Reference standard does not match protocol (asthma defined as affirmative answer to 'has a doctor ever said this child has asthma' or 3 out of 4 wheezing symptoms on questionnaire)
FORTUNA 2007[505]	Methacholine used as reference standard - sn/sp of FeNO, eos, spirometry and BDR with positive methacholine test used to diagnose asthma
FRANKLIN 2003[514]	Population does not match protocol (all asymptomatic at time of the study)
FRUCHTER 2009[524]	Reference standard does not match protocol - not physician diagnosis and objective test
GADE 2009[531]	Does not match review question (influence of mannitol and methacholine tests on each other)
GARCIA-RIO 2004[543]	Population does not match protocol – all had positive histamine challenge
GHODRATI 2011[556]	Not in English
GILBERT 1990[564]	No relevant outcomes and does not match review question (healthy controls and people with confirmed asthma with no comparator test)
GODFREY 1999[571]	No relevant outcomes and does not match

Reference	Reason for exclusion
	review question (healthy controls and people with confirmed asthma with no comparator test)
GOLDSTEIN 1994[579]	Reference standard does not match protocol – based on symptoms and response to therapy (no objective test)
GOLDSTEIN 2001[580]	Does not match review question – longitudinal follow-up to asthma diagnosis and methacholine test used as part of reference standard to Dx asthma
GRAIF 2002[584]	Sn/sp of SPT with positive methacholine test used to diagnose asthma (no reference standard of physician Dx to calculate sn/sp of methacholine test)
GREENSPON 1992[592]	Reference standard does not match protocol – Dx asthma group gave a history typical of asthma and had histories of acute exacerbation that were relieved by bronchodilator therapy
GRUCHALLA 2003[595]	Reference standard does not match protocol – methacholine used as part of Dx of asthma for calculation of sn/sp of symptoms questionnaire in the Dx of asthma
HIGGINS 1992[669]	Reference standard does not match protocol – Dx based on symptoms questionnaire or 'ever had asthma attack' (no mention of objective test)
HOPP 1984[693]	No relevant outcomes and does not match review question (healthy controls and people with confirmed asthma with no comparator test).
HUNTER 2002[713]	Methacholine challenge tests used as one of the objective tests to Dx asthma in the group with asthma
HUR 2009[716]	Conference abstract
HUR 2010[714]	Conference abstract – duplicate of Hur 2010
IRWIN 1997[732]	Population does not match protocol – all symptomatic and methacholine challenge positive
JAMES 1992[743]	Reference standard does not match protocol (physician Dx without objective test and/or wheeze in the last 12 months)
JAMES 1997[744]	Review article – summarises studies sn/sp of challenge tests but ref standard does not match protocol (use symptom questionnaire and diagnosis based on wheeze in last 12 months or asthma Dx by doctor)
JOHNSON 1987[771]	Reference standard does not match protocol – association of methacholine

Reference	Reason for exclusion
	response with symptoms not physician Dx
JOSEPH 2004[783]	Reference standard does not match protocol; physician diagnosis + symptoms of wheeze in last 12 months + asthma meds in last 12 months (no objective test)
KANG 2005[810]	No relevant outcomes and does not match review question (people with confirmed asthma with no comparator test)
KHALID 2009[848]	Sn/sp of different measure for methacholine challenge (with PC20 positive/negative used for asthma Dx)
KIM 2002[863]	Reference standard does not match protocol (correlation of BHR with risk factors and symptoms from questionnaire – no physician Dx)
KIM 2014A[862]	Conference abstract
KIM 2014B[860]	Case control study
KING 1989[866]	Index test and reference standard do not match protocol – sn/sp of wheezing on max forced exhalation as predictor of positive methacholine test
KIVASTIK 2007[870]	Population does not match protocol (age range 3-6 years)
KNOX 1989[883]	No relevant outcomes and does not match review question (different methods of measuring methacholine response)
KOLNAAR 1995[894]	Reference standard does not match protocol - comparison of histamine test to presence of asthma symptoms (not to physician Dx)
LAU 2002[963]	Population does not match protocol – general population
LEE 2011[973]	Conference abstract
LEVIN 2011[990]	Reference standard does not match protocol - self-reported symptoms of asthma in the last 12 months
LEWIS 2001[994]	Reference standard does not match protocol - self reported doctor-Dx asthma and no mention of objective test
LIEM 2008[1002]	No relevant outcomes and does not match review question (healthy controls and people with confirmed asthma with no comparator test)
LINNA 1998[1013]	All patients with asthma and no comparator test (comparing different methods of measuring methacholine challenge)
LUMELLI 2010[1035]	Conference abstract
MADSEN 1985[1045]	Reference standard does not match protocol – some patients were Dx without objective test on basis of answer to 2

Reference	Reason for exclusion
	questions on attacks of shortness of breath
MADSEN 1986[1044]	Reference standard does not match protocol – some patients were Dx without objective test on basis of answer to 2 questions on attacks of shortness of breath
MALMBERG 2001[1063]	No relevant outcomes and does not match review question (people with confirmed asthma with no comparator test)
MANNINO 1996[1073]	Methacholine challenge test but no comparator or reference standard test
MANSO 2011[1074]	Reference standard does not match protocol – methacholine test used as reference standard to Dx asthma in some patients
MCCLEAN 2010[1099]	No relevant outcomes and does not match review question (healthy controls and people with confirmed asthma with no comparator test). Physician diagnosis without objective test
MCGARVEY 1998[1106]	No relevant outcomes and does not match review question - histamine challenge in comparison to treatment response for various respiratory diseases
METSO 1996[1126]	Reference standard does not match protocol
MIEDINGER 2010[1133]	Reference standard does not match protocol – not all patients Dx with asthma had an objective test (some physician Dx only)
MULLER 1993[1176]	Case control study
NADASKIC 2010[1191]	Conference abstract
NICKELS 2014[1219]	Conference abstract
NIGGEMANN 2001[1230]	Reference standard does not match protocol - sn/sp if histamine challenge to predict asthma symptoms (not diagnosis of asthma)
NISH 1992[1237]	Reference standard does not match protocol – physician Dx with objective test not reported and histamine challenge used as part of reference standard to Dx
OCONNOR 1994[1252]	Reference standard does not match protocol - affirmative response to 'have you ever had asthma?'
OHKURA 2013[1262]	Conference abstract
OKUPA 2012[1266]	Conference abstract
PALMEIRO 1992[1284]	Reference standard does not match protocol – asthma Dx based on questionnaire reponses
PARAMESWARAN 1999[1293]	Reference standard does not match protocol - physian Dx without objective test

Reference	Reason for exclusion
PARK 2009[1300]	Conference abstract
PARKER 2004[1302]	Population does not match protocol (all patients had positive methacholine challenge test and looking at factors which influence the PC20)
PARKERSON 2011[1303]	Review article
PATTEMORE 1990[1307]	Reference standard does not match protocol (asthma diagnosis by previous report of a diagnosis but no objective test)
PEDROSA 2009[1315]	Index test and reference standard do not match protocol – methacholine test used as reference standard to Dx asthma and assess sn/sp of AMP challenge
PEDROSA 2010[1316]	Index test and reference standard do not match protocol – methacholine test used as reference standard to Dx asthma and assess sn/sp of FeNO
PERPINA 1993[1322]	Case control type study with 4 groups (asthma; rhinitis; chronic bronchitis; healthy controls) – study gives sn/sp values for MCT but this is basedall patients (includes asymptomatic healthy control group)
POPA 1988[1366]	No relevant outcomes and does not match review question (healthy controls and people with confirmed asthma with no comparator test).
PORSBJERG 2007[1368]	Population does not match protocol – relationship between the response to methacholine and mannitol in asymptomatic subjects who do not have asthma
PORSBJERG 2009[1369]	Review article
PRATTER 1983[1383]	Index test and reference standard do not match protocol – sn/sp of wheeze symptoms vs reference standard of physician Dx with methacholine test
PRIETO 1998[1391]	Index test and reference standard do not match protocol – methacholine test used as reference standard to Dx asthma and assess sn/sp of PEFV
PRIETO 1998A[1390]	No relevant outcomes and does not match review question (differences in dose-response curve to methacholine in asthma, rhinitis and controls)
PUOLIJOKI 1992[1400]	Population does not match protocol – all methacholine challenge test negative patients
PUROKIVI 2007[1401]	Index test does not match protocol – hypertonic histamine challenge
REMES 2002[1433]	Methacholine challenge tests used as one of

Reference	Reason for exclusion
	the objective tests to Dx asthma
RENWICK 1996[1436]	Chronic airway obstruction prevelence and BDR
RIJCKEN 1989[1447]	Reference standard does not match protocol (sensitivity and specificity of histamine challenge test to detect self-reported symptoms (symptomatic or asymptomatic)
ROQUET 1996[1464]	No relevant outcomes and does not match review question –sn/sp of Eos to predict positive challenge test
SACHOLSEN 2010[1482]	Population does not match protocol - general population not all people with asthma or suspected asthma
SCHLEICH 2012[1514]	Methacholine challenge test used as part of the reference standard to Dx asthma in suspected asthma patients without airway obstruction or BDR
SCHMIDT 1992[1516]	All patients with asthma and no comparator test (comparing different methods of histamine challenge). Physician Dx only, no objective test
SCHNEIDER 2009A[1519]	Methacholine challenge test used as part of the reference standard to Dx asthma and assess the sn/sp of spirometry in GP
SCHULZE 2013[1527]	No relevant outcomes and does not match review question – sn/sp of methacholine challenge to detect a positive allergen response
SHAPIRO 1982[1555]	Reference standard does not match protocol – methacholine test used as reference standard to Dx asthma
SIERSTED 1994[1573]	Reference standard does not match protocol – asthma Dx based on questionnaire responses to doctor diagnosed asthma and symptoms (no mention of objective test)
SIERSTED 1994[1573]	Duplicate – ordered twice, already excluded for this review
SIERSTED 1996[1574]	Reference standard does not match protocol – methacholine test used as part of reference standard to Dx asthma
SISTEK 2006[1601]	Reference standard does not match protocol – asthma Dx based on questionnaire responses to doctor diagnosed asthma and attack in the last 12 months (no mention of objective test)
SORIANO 1999[1627]	Reference standard does not match protocol - positive methacholine test used to Dx asthma
SOVIJARVI 1986[1634]	No relevant outcomes and does not match

Reference	Reason for exclusion
	review question – different methods of measuring methacholine test
SPIROPOULOS 1986[1641]	No relevant outcomes and does not match review question – sn/sp of methacholine test in predicting hyper-reative airway symptoms not physician Dx of asthma
SPOSATO 2014[1644]	Index test and reference standard do not match protocol
SPRINGER 2000[1645]	Population does not match protocol (aged 2-8 years). All people with confirmed asthma and no comparator test
STAHL 2009[1651]	Conference abstract
SUN 2007[318]	Duplicate of CHOI 2007A – already excluded in this review
SVERRILD 2009 [1689]	Same data used for Sverrild 2010 paper already excluded from this review.
SVERRILD 2010[1688]	Reference standard does not match protocol - physician Dx without objective test (physician Dx made on the basis of symptoms in the last 12 months in combination with either a eNO level of greater than 30 ppb, a history of allergic rhinoconjunctivitis, dermatitis, a positive skin prick test response, a familial predisposition to atopic disease, nonallergic rhinoconjunctivitis, or an FEV1/forced vital capacity ratio of less than 75%).
SVERRILD 2012[1687]	Review article
SVERRILD 2013[1686]	Sn/sp of FeNO in predicting positive mannitol response. Reference standard does not match protocol - physian Dx with no mention of objective test
TAKAMI 2013[1699]	No relevant outcomes and does not match review question (correlation study)
TERNESTEN 2002[1723]	Methacholine challenge test used as part of the reference standard to Dx asthma
TIE 2012[1736]	Reference standard does not match protocol
TODD 2004[1745]	Not relevant outcomes and does not answer review question - all people with asthma with positive methacholine challange (comparing methods of performing methacholine test)
TOELLE 1992[1746]	Methacholine challenge test used as part of the reference standard to Dx asthma
TOWNLEY 1975[1762]	Reference standard does not match protocol – no objective test
TOWNLEY 1990[1761]	Can only calculate sensitivity (methacholine challenge in suspected asthma and asymptomatic controls – all suspected

Reference	Reason for exclusion
	group were Dx based on reference standard and no Dx of control group reported)
VILOZNI 2009[1846]	Population does not match protocol (aged 3-6 years)
WONGTIM 1997[1913]	Methacholine challenge test used as part of the reference standard to Dx asthma
WOO 2012[1914]	Methacholine challenge test used as part of the reference standard to Dx asthma – Dx based on symptoms and BDR and/or positive methacholine challenge
WOOLCOCK 1984[1920]	Histamine challenge test but no comparator or reference standard test (looking at dose-response curve to histamine in people with asthma and controls)
WU 2011[1923]	Conference abstract
XU 2001[1926]	Reference standard does not match protocol - asthma was defined as a history of physician-diagnosed asthma at any time in the past (no mention of objective test)
YURDAKUL 2005[1945]	Reference standard does not match protocol – methacholine test used as part of reference standard to Dx asthma
ZAGHLOUL 2009[1947]	Conference abstract

K.14 Diagnosis: Mannitol challenge test

Table 222: Studies excluded from the clinical review

Reference	Reason for exclusion
ALBERTS 1994[32]	Index test and reference standard do not match protocol – sn/sp of FEF25-75% in predicting positive methacholine test
ALBORNOZ 1995[33]	All people with confirmed asthma and no comparator test
ALVAREZPUEBLA 2003[40]	Reference standard does not match protocol (Dx based on symptoms without objective test)
ANDERSON 2010A[46]	Conference abstract
ANDERSON 2011[47]	Review article
ANDREGNETTE 2011[49]	Conference abstract
ANTOLINAMERIGO 2012[54]	Conference abstract
ANTOLINAMERIGO 2013[55]	Conference abstract
AVITAL 1995[82]	Population does not match protocol – mean age < 5years
AVITAL 1995A[83]	Comparator tests do not match protocol (methacholine vs AMP and exercise) and sn/sp of methacholine not compared to reference standard of physician Dx with

Reference	Reason for exclusion
	objective test (American Thoracic Soc diagnostic criteria for asthma)
BACKER 1991[88]	Reference standard does not match protocol – questionnaire based on symptoms and physician Dx without report of objective test
BACKER 1992[91]	No relevant outcomes and does not match review question - relationship between bronchial responsiveness and IgE
BACKER 1992B[90]	Index test does not match protocol (sn and sp of physician Dx and symptoms in relation to exercise challenge)
BACKER 1995[87]	Population does not match protocol - prevelence of positive HCT in general population and correlation with asthma and atopy
BACKER 2014[92]	Index test and reference standard do not match protocol – sn/sp of FeNO to predict positive mannitol in suspected asthma (not physician diagnosis and objective test)
BAILLY 2011[94]	No relevant outcomes and does not match review question (different methods of measuring methacholine response, Pc20 used as part of reference standard for Dx)
BALLWEG 2012[100]	Review article
BARBEN 2011[107]	Reference standard does not match protocol – sn/sp for Mannitol test only calculated taking into account index test result. Can calculated sn/sp of mannitol vs exercise test in children but this is only in suspected asthma (cannot do calculation for those children Dx according to the RS)
BASIR 1995[124]	No reference standard of physician diagnosis with objective test
BENNETT 1987[153]	No relevant outcomes and does not match review question (different methods of measuring methacholine and histamine response; all people with confirmed asthma and comparator does not match protocol)
BERKMAN 2005[160]	Reference standard does not match protocol – physician Dx without objective test in a proportion of patients and no data on the percentage of patients who were Dx with an objective test.
BEYDON 2008[168]	No relevant outcomes and does not match review question – correlation between BDR and methacholine response
BIBI 1991[172]	Index test does not match protocol – methacholine challenge test
BIRNBAUM 2007[175]	Review article
BONAVIA 1996[186]	Comparator tests and reference standard

Reference	Reason for exclusion
	do not match protocol (asthma group defined by symptom score not physician Dx)
BOONSAWAT 1992[191]	Reference standard does not match protocol (physician Dx without objective test)
BOUAZIZ 1996[200]	Comparing different methods of measuring methacholine test (all patients with asthma and no comparator test)
BRAND 1993[215]	Index test does not match protocol – no challenge test performed
BRUSCHI 1989[236]	Population does not match protocol - general population not suspected asthma
BUSSE 2005[255]	Review / report from workshop
CARLSEN 1998[275]	case-control study
CARLSTEN 2011[277]	Reference standard does not match protocol – Dx was clinical decision made by the paediatric allergist based on symptoms of wheeze and cough, use of medications and physical findings
CHATHAM 1982[303]	Sn/sp of histamine and methacholine vs exercise in people with asthma and controls (does not match this protocol comparator). No reference standard of physician Dx with objective test.
CHOI 2003[316]	Index test does not match protocol – methacholine challenge test
CHOI 2007A[318]	Population does not match protocol (all patients had positive methacholine challenge test)
CHUNG 2010[326]	Conference abstract – sn/sp of mannitol and methacholine but reference standard not mentioned
CIPRANDI 2010[333]	No relevant outcomes and does not match review question – correlation between FeNO and methacholine PC20 and sn/sp of FeNO to predict positive methacholine test
CIPRANDI 2011[331]	Population does not match protocol – all Dx with allergic rhinitis and excluded if a history of asthma or referred with asthma symptoms
CIRILLO 2009[336]	Population does not match protocol – all Dx with allergic rhinitis and excluded if a history of asthma or referred with asthma symptoms
COCKCROFT 1979[352]	No relevant outcomes and does not match review question (correlation between allergen PC20 and histamine PC20 in people with confirmed asthma)
COCKCROFT 1992[351]	Reference standard does not match protocol – Dx based on questionnaire

Reference	Reason for exclusion
	(previous doctor diagnosis or wheeze symptoms)
COCKCROFT 2005[350]	No relevant outcomes and does not match review question (correlation between allergen, histamine and methacholine PC20 in people with confirmed asthma)
COCKCROFT 2009[353]	Review article
COCKCROFT 2010[354]	Review article check for refs
CORDEIRO 2011[360]	Index test and reference standard do not match protocol – histamine test used as part of reference standard to Dx (index test = FeNO)
DEHAUT 1983[407]	No relevant outcomes and does not match review question (different methods of measuring histamine response)
DELGIUDICE 2004[409]	No relevant outcomes and does not match review question – correlation between FeNO and PC20 (all patients with asthma but Dx made by physician with no objective test)
DI LORENZO 2007[432]	Case control type study with 3 groups (asthma Dx by symptoms and objective test; gastro-oesophageal reflux group with asthma symptoms; healthy controls) – study gives sn/sp values for MCT but this is based on 52% of patients having asthma (includes asymptomatic healthy control group)
DREWEK 2009[450]	Index test does not match protocol (sn and sp of FEF25-75 to measure methacholine response; diagnosis of asthma based on symptoms during challenge test)
DURAND 2011[454]	Conference abstract – reference standard not mentioned
DURZO 2012[384]	Conference abstract
FORASTIERE 1991[502]	Reference standard does not match protocol (asthma defined as affirmative answer to 'has a doctor ever said this child has asthma' or 3 out of 4 wheezing symptoms on questionnaire)
FORTUNA 2007[505]	Methacholine used as reference standard - sn/sp of FeNO, eos, spirometry and BDR with positive methacholine test used to diagnose asthma
FRANKLIN 2003[514]	Population does not match protocol (all asymptomatic at time of the study)
FRUCHTER 2009[524]	Index test and reference standard do not match protocol – sn/sp of BDR to predict positive methacholine in suspected asthma (not physician diagnosis and objective test)
GADE 2009[531]	Does not match review question (influence of mannitol and methacholine tests on each

Reference	Reason for exclusion
	other)
GARCIA-RIO 2004[543]	Population does not match protocol – all had positive histamine challenge
GHODRATI 2011[556]	Not in English
GILBERT 1990[564]	No relevant outcomes and does not match review question (healthy controls and people with confirmed asthma with no comparator test)
GODFREY 1999[571]	No relevant outcomes and does not match review question (healthy controls and people with confirmed asthma with no comparator test)
GOLDSTEIN 1994[579]	Index test does not match protocol – methacholine challenge test
GOLDSTEIN 2001[580]	Does not match review question – longitudinal follow-up to asthma diagnosis and methacholine test used as part of reference standard to Dx asthma
GRAIF 2002[584]	Sn/sp of SPT with positive methacholine test used to diagnose asthma (no reference standard of physician Dx to calculate sn/sp of methacholine test)
GREENSPON 1992[592]	Reference standard does not match protocol – Dx asthma group gave a history typical of asthma and had histories of acute exacerbation that were relieved by bronchodilator therapy
GRUCHALLA 2003[595]	Reference standard does not match protocol – methacholine used as part of Dx of asthma for calculation of sn/sp of symptoms questionnaire in the Dx of asthma
HEDMAN 1998[647]	Index test does not match protocol – methacholine challenge test
HIGGINS 1992[669]	Reference standard does not match protocol – Dx based on symptoms questionnaire or 'ever had asthma attack' (no mention of objective test)
HOPP 1984[693]	No relevant outcomes and does not match review question (healthy controls and people with confirmed asthma with no comparator test).
HUNTER 2002[713]	Methacholine challenge tests used as one of the objective tests to Dx asthma in the group with asthma
HUR 2009[716]	Conference abstract
HUR 2010[714]	Conference abstract – duplicate of Hur 2010
IRWIN 1997[732]	Population does not match protocol – all symptomatic and methacholine challenge positive

Reference	Reason for exclusion
JAMES 1992[743]	Reference standard does not match protocol (physician Dx without objective test and/or wheeze in the last 12 months)
JAMES 1997[744]	Review article – summarises studies sn/sp of challenge tests but ref standard does not match protocol (use symptom questionnaire and diagnosis based on wheeze in last 12 months or asthma Dx by doctor)
JOHNSON 1987[771]	Reference standard does not match protocol – association of methacholine response with symptoms not physician Dx
JOSEPH 2004[783]	Reference standard does not match protocol; physician diagnosis + symptoms of wheeze in last 12 months + asthma meds in last 12 months (no objective test)
KANG 2005[810]	No relevant outcomes and does not match review question (people with confirmed asthma with no comparator test)
KHALID 2009[848]	Sn/sp of different measure for methacholine challenge (with PC20 positive/negative used for asthma Dx)
KIM 2002[863]	Reference standard does not match protocol (correlation of BHR with risk factors and symptoms from questionnaire – no physician Dx)
KIM 2014[860]	Case control study
KIM 2014A[862]	Conference abstract
KING 1989[866]	Index test and reference standard do not match protocol – sn/sp of wheezing on max forced exhalation as predictor of positive methacholine test
KIVASTIK 2007[870]	Population does not match protocol (age range 3-6 years)
KNOX 1989[883]	No relevant outcomes and does not match review question (different methods of measuring methacholine response)
KOLNAAR 1995[894]	Reference standard does not match protocol - comparison of histamine test to presence of asthma symptoms (not to physician Dx)
KOSKELA 2003[905]	All patients with asthma and comparator test does not match protocol (comparators histamine and cold air challenge tests)
KOWAL 2009[914]	Index test does not match protocol – histamine challenge test
LEE 2011[973]	Conference abstract
LEVIN 2011[990]	Reference standard does not match protocol - self-reported symptoms of asthma in the last 12 months

Reference	Reason for exclusion
LEWIS 2001[994]	Reference standard does not match protocol - self reported doctor-Dx asthma and no mention of objective test
LIEM 2008[1002]	No relevant outcomes and does not match review question (healthy controls and people with confirmed asthma with no comparator test)
LINNA 1998[1013]	All patients with asthma and no comparator test (comparing different methods of measuring methacholine challenge)
LUMELLI 2010[1035]	Conference abstract
MADSEN 1985[1045]	Reference standard does not match protocol – some patients were Dx without objective test on basis of answer to 2 questions on attacks of shortness of breath
MADSEN 1986[1044]	Reference standard does not match protocol – some patients were Dx without objective test on basis of answer to 2 questions on attacks of shortness of breath
MALMBERG 2001[1063]	No relevant outcomes and does not match review question (people with confirmed asthma with no comparator test)
MANNINO 1996[1073]	Methacholine challenge test but no comparator or reference standard test
MANSO 2011[1074]	Reference standard does not match protocol – methacholine test used as reference standard to Dx asthma in some patients
MCCLEAN 2010[1099]	No relevant outcomes and does not match review question (healthy controls and people with confirmed asthma with no comparator test). Physician diagnosis without objective test
MCGARVEY 1998[1106]	No relevant outcomes and does not match review question - histamine challenge in comparison to treatment response for various respiratory diseases
METSO 1996[1126]	Reference standard does not match protocol
MIEDINGER 2010[1133]	Reference standard does not match protocol – not all patients Dx with asthma had an objective test (some physician Dx only)
MULLER 1993[1176]	Case control study
NADASKIC 2010[1191]	Conference abstract
NICKELS 2014[1219]	Conference abstract
NIEMINEN 1992[1229]	Index test does not match protocol – methacholine challenge test
NIGGEMANN 2001[1230]	Reference standard does not match protocol - sn/sp if histamine challenge to

Reference	Reason for exclusion
	predict asthma symptoms (not diagnosis of asthma)
NISH 1992[1237]	Reference standard does not match protocol – physician Dx with objective test not reported and histamine challenge used as part of reference standard to Dx
OCONNOR 1994[1252]	Reference standard does not match protocol - affirmative response to 'have you ever had asthma?'
OHKURA 2013[1262]	Conference abstract
OKUPA 2012[1266]	Conference abstract
OTTER 1997[417]	Index test does not match protocol – histamine challenge test
PALMEIRO 1992[1284]	Reference standard does not match protocol – asthma Dx based on questionnaire reponses
PARAMESWARAN 1999[1293]	Reference standard does not match protocol - physian Dx without objective test
PARK 2009[1300]	Conference abstract
PARKER 2004[1302]	Population does not match protocol (all patients had positive methacholine challenge test and looking at factors which influence the PC20)
PARKERSON 2011[1303]	Review article
PATTEMORE 1990[1307]	Reference standard does not match protocol (asthma diagnosis by previous report of a diagnosis but no objective test)
PEDROSA 2009[1315]	Index test and reference standard do not match protocol – methacholine test used as reference standard to Dx asthma and assess sn/sp of AMP challenge
PEDROSA 2010[1316]	Index test and reference standard do not match protocol – methacholine test used as reference standard to Dx asthma and assess sn/sp of FeNO
PERPINA 1993[1322]	Case control type study with 4 groups (asthma; rhinitis; chronic bronchitis; healthy controls) – study gives sn/sp values for MCT but this is basedall patients (includes asymptomatic healthy control group)
POPA 1988[1366]	No relevant outcomes and does not match review question (healthy controls and people with confirmed asthma with no comparator test).
PORSBJERG 2007[1368]	Population does not match protocol – relationship between the response to methacholine and mannitol in asymptomatic subjects who do not have asthma
PORSBJERG 2009[1369]	Review article

Reference	Reason for exclusion
PRATTER 1983[1383]	Index test and reference standard do not match protocol – sn/sp of wheeze symptoms vs reference standard of physician Dx with methacholine test
PRIETO 1998[1391]	Index test and reference standard do not match protocol – methacholine test used as reference standard to Dx asthma and assess sn/sp of PEFV
PRIETO 1998A[1390]	No relevant outcomes and does not match review question (differences in dose-response curve to methacholine in asthma, rhinitis and controls)
PUOLIJOKI 1992[1400]	Population does not match protocol – all methacholine challenge test negative patients
PUROKIVI 2007[1401]	Index test does not match protocol – histamine challenge test
REMES 2002[1433]	Methacholine challenge tests used as one of the objective tests to Dx asthma
RENWICK 1996[1436]	Chronic airway obstruction prevelence and BDR
RIJCKEN 1989[1447]	Reference standard does not match protocol (sensitivity and specificity of histamine challenge test to detect self-reported symptoms (symptomatic or asymptomatic)
ROQUET 1996[1464]	No relevant outcomes and does not match review question –sn/sp of Eos to predict positive challenge test
SACHOLSEN 2010[1482]	Population does not match protocol - general population not all with asthma or suspected asthma
SCHLEICH 2012[1514]	Methacholine challenge test used as part of the reference standard to Dx asthma in suspected asthma patients without airway obstruction or BDR
SCHMIDT 1992[1516]	All patients with asthma and no comparator test (comparing different methods of histamine challenge). Physician Dx only, no objective test
SCHNEIDER 2009A[1519]	Methacholine challenge test used as part of the reference standard to Dx asthma and assess the sn/sp of spirometry in GP
SCHULZE 2013[1527]	No relevant outcomes and does not match review question – sn/sp of methacholine challenge to detect a positive allergen response
SHAPIRO 1982[1555]	Reference standard does not match protocol – methacholine test used as reference standard to Dx asthma

Reference	Reason for exclusion
SIERSTED 1994[1573]	Reference standard does not match protocol – asthma Dx based on questionnaire responses to doctor diagnosed asthma and symptoms (no mention of objective test)
SIERSTED 1994[1573]	Duplicate – ordered twice, already excluded for this review
SIERSTED 1996[1574]	Reference standard does not match protocol – methacholine test used as part of reference standard to Dx asthma
SISTEK 2006[1601]	Reference standard does not match protocol – asthma Dx based on questionnaire responses to doctor diagnosed asthma and attack in the last 12 months (no mention of objective test)
SORIANO 1999[1627]	Reference standard does not match protocol - positive methacholine test used to Dx asthma
SOVIJARVI 1986[1634]	No relevant outcomes and does not match review question – different methods of measuring methacholine test
SPIROPOULOS 1986[1641]	No relevant outcomes and does not match review question – sn/sp of methacholine test in predicting hyper-reative airway symptoms not physician Dx of asthma
SPOSATO 2014[1644]	Index test and reference standard do not match protocol
SPRINGER 2000[1645]	Population does not match protocol (aged 2-8 years). All people with confirmed asthma and no comparator test
STAHL 2009[1651]	Conference abstract
SUN 2007[318]	Duplicate of CHOI 2007A – already excluded in this review
SVERRILD 2009 [1689]	Same data used for Sverrild 2010 paper already excluded from this review.
SVERRILD 2010[1688]	Reference standard does not match protocol - physician Dx without objective test (physician Dx made on the basis of symptoms in the last 12 months in combination with either a eNO level of greater than 30 ppb, a history of allergic rhinoconjunctivitis, dermatitis, a positive skin prick test response, a familial predisposition to atopic disease, nonallergic rhinoconjunctivitis, or an FEV1/forced vital capacity ratio of less than 75%).
SVERRILD 2012[1687]	Review article
SVERRILD 2013[1686]	sn/sp of FeNO in predicting positive mannitol response. Reference standard does not match protocol - physian Dx with no mention of objective test

Reference	Reason for exclusion
TAKAMI 2013[1699]	No relevant outcomes and does not match review question (correlation study)
TERNESTEN 2002[1723]	Methacholine challenge test used as part of the reference standard to Dx asthma
TIE 2012[1736]	Reference standard does not match protocol
TODD 2004[1745]	Not relevant outcomes and does not answer review question - all people with asthma with positive methacholine challange (comparing methods of performing methacholine test)
TOELLE 1992[1746]	Methacholine challenge test used as part of the reference standard to Dx asthma
TOWNLEY 1975[1762]	Reference standard does not match protocol – no objective test
TOWNLEY 1990[1761]	Can only calculate sensitivity (methacholine challenge in suspected asthma and asymptomatic controls – all suspected group were Dx based on reference standard and no Dx of control group reported)
VILOZNI 2009[1846]	Population does not match protocol (aged 3-6 years)
WONGTIM 1997[1913]	Methacholine challenge test used as part of the reference standard to Dx asthma
WOO 2012[1914]	Methacholine challenge test used as part of the reference standard to Dx asthma – Dx based on symptoms and BDR and/or positive methacholine challenge
WOOLCOCK 1984[1920]	Histamine challenge test but no comparator or reference standard test (looking at dose-response curve to histamine in people with asthma and controls)
WU 2011[1923]	Conference abstract
XU 2001[1926]	Reference standard does not match protocol - asthma was defined as a history of physician-diagnosed asthma at any time in the past (no mention of objective test)
YURDAKUL 2005[1945]	Reference standard does not match protocol – methacholine test used as part of reference standard to Dx asthma
ZAGHLOUL 2009[1947]	Conference abstract

K.15 Diagnosis: Exercise challenge test

Table 223: Studies excluded from the clinical review

Reference	Reason for exclusion
ALBERTS1994[32]	Not exercise test
ANDERSON2009[48]	Exercise test as gold standard not index test

Reference	Reason for exclusion
ANDERSON2010A[46]	Exercise test as gold standard not index test
ANDERSON2011[47]	Not primary study
ANSLEY2012[53]	Not exercise test
ARIASIRIGOYEN1999[65]	Case control study
AVITAL 1995A[83]	Wrong cut-off value: Change in FEV1 of 5% is very low.
AVITAL1995[82]	Mean age <5 years
BACKER 1992[90]	Wrong population: general population, not suspected asthma.
BACKER1991[88]	Not exercise test +/- versus histamine challenge +/- or diagnosis of asthma
BAILLY2011[94]	Not exercise
BARBEN2011[107]	Exercise test as gold standard not index test
BELCHER1987[144]	Not exercise test to diagnose asthma (refractoriness to second test)
BENARB 2011[150]	Wrong reference standard: ISAAC questionnaire but no objective test.
BENNETT1987[153]	Not exercise
BERKMAN 2005[160]	Wrong reference standard: physician Dx but no objective test.
BEYDON2008[168]	Not exercise
BHAGAT1984[169]	Not exercise test over/under threshold versus comparator
BLACKIE1990[179]	Review not primary study
BOCCACCINO2007[183]	No comparator test of diagnosis of asthma/no asthma
BORGES2011[192]	Review not primary study
BOUGAULT2010[202]	Not exercise test
BRANNAN2012[219]	Review not primary study
BROZEK2009[234]	Case control study
BUCHVALD2005[241]	Exercise test as gold standard not index test
CALVERT2005[265]	Case control study
CAREY2010[271]	Not diagnosis of asthma (healthy subjects)
CARLSEN 1998[275]	Wrong reference standard: physician Dx but no objective test.
CARLSEN2002[276]	Not primary study
CARLSTEN2011[277]	Not exercise test
CHATHAM1982[303]	Unclear cut-offs. Case-control study
CHEN2014[307]	Population does not match protocol – general population
CHOI2005[317]	EIB as outcome not index test

Reference	Reason for exclusion
CLEARIE2010[339]	Elite athletes
COCKCROFT1992[351]	Not exercise test
COCKCROFT2009[353]	SR not primary study - no data presented
COCKCROFT2009A[349]	Review not primary study
COCKCROFT2010[354]	Not a primary study – no data presented
DEMISSIE 1998[416]	Wrong reference standard: physician Dx but no objective test.
DICKINSON2006[438]	Elite athletes
DICKINSON2006A[437]	Elite athletes
DOR1999[444]	Non-English
DRYDEN2010[453]	Exercise test as gold standard not index test
ELHALAWANI2003[468]	Exercise test as gold standard not index test
ELIASSON1992[469]	Case control study
FEITOSA2012[488]	Exercise test as gold standard not index test
FUENTES2011[525]	Case control study
GARCIADELARUBIA1998[540]	Case control study
GARCIARIO2004[543]	Not exercise test
GERALD2002[551]	Information on subjects with positive exercise test only, not those with negative test
GIFT1994[561]	Commentary not primary study
GODFREY1999[571]	Compares outcome of exercise test in subjects with asthma against previously published studies in normal populations; data for test results comparing exercise with methacholine challenge within asthma group not shown
GRUCHALLA2003[595]	Case control study and not all participants had exercise test
GRUCHALLA2009[596]	Not exercise test
GRZELEWSKI2012[599]	Exercise test as gold standard not index test
HOLZER2002[687]	Not exercise test as index test
HOLZER2003[686]	Not exercise test as index test
HOPP1984[693]	Not exercise test
HORIE1983[700]	Not exercise positive/negative versus asthma diagnosis or other test positive/ negative
JOHNSON1987[771]	Not exercise test
JONES1994[774]	Case control study with longitudinal follow up
JONES1994A[775]	Case control study

Reference	Reason for exclusion
JOOS2003[778]	Review not primary study
KANAZAWA2002[808]	Not exercise test +/- versus asthma diagnosis or other test
KANNISTO2000[811]	No data on exercise +/- versus comparator
KING1989[866]	Not exercise test
KIVILOOG 1975[871]	Wrong outcome measure: not a standard measure (change in PEFR ≥15%)
KNOX1989[883]	Not exercise test
KOH1996[887]	Not exercise +/- versus comparator +/-`
KOH1998[886]	Not exercise +/- versus comparator +/-`
KOTANIEMISYRJANEN2002[907]	Exercise test part of gold standard not index test
LAZOVELASQUEZ2005[968]	Case control study
LEX2007[995]	Exercise test as gold standard not index test
LIEM2008[1002]	Not exercise test
LUNTSOV2012[1036]	Not exercise +/- versus comparator +/-`
MADSEN1985[1045]	Not exercise test
MADSEN1986[1044]	Not exercise test
MALMBERG2009[1065]	Exercise test as gold standard not index test
MANSO2011[1074]	Not exercise test
MIEDINGER2010[1133]	Case control study
MODL 1995[1154]	Wrong population: symptom-free and medication-free people with asthma
MULLER 1993[1176]	Not exercise test
MUSSAFFI1986[1187]	Not exercise +/- versus comparator +/-`
NEIJENS1983[1207]	Review not primary study
NISH1992[1237]	Exercise test as part of gold standard not index test
NISHIO2007[1238]	Exercise test as gold standard not index test
OBATA1994[1253]	Case control study
PEDROSA2009[1315]	Not exercise test
PONSONBY 1996[1363]	Wrong reference standard: ISAAC questionnaire but no objective test.
PORSBJERG2009[1369]	Not primary study
PRATTER1989[1382]	Not all patients had exercise test and exercise test part of gold standard not index
PUOLIJOKI1992[1400]	Not exercise test
RAMSER2008[1413]	Exercise test as gold standard not index test

Reference	Reason for exclusion
RANDOLPH2011[1415]	Review not primary study
RANDOLPH2011A[1417]	Unclear what is the gold standard
REMES 2002[1433]	Wrong reference standard: physician Dx but no objective test.
RIEDLER1992A[1443]	Non-English
RIEDLER1994[1444]	Case control study
RIEDLER1997[1442]	Review, not primary study.
ROMBERG2011[1459]	Elite athletes
ROMBERG2012[1460]	Elite athletes
ROUHOS2010[1471]	Exercise test mentioned but results not reported
RUNDELL2004[1476]	Exercise = index test but also part of gold standard
SACHSOLSEN2010[1482]	Exercise test as part of gold standard not index test
SACHSOLSEN2013[1483]	Case control study
SCOLLO2000[1532]	Exercise test as gold standard not index test
SHAPIRO1982[1555]	Not exercise test
SIERSTED 1996[1574]	Wrong population: general population, not suspected asthma.
SIN2009[1593]	Data versus methacholine test was not all in asthma patients; data versus diagnosis not calculable
SINCLAIR1995[1595]	Exercise test as both index and comparison test
SMITH1990[1614]	Exercise test as gold standard not index test
SOTORAMOS2013[1632]	Comparator test is FeNO – not on list in protocol
SOVIJARVI1986[1634]	Not exercise test
SPIERING2004[1640]	Exercise test as gold standard not index test
SPIROPOULOS1986[1641]	Not exercise test
STICKLAND2011[1661]	Review, not primary study. Exercise test as gold standard not index test
TAL1984[1701]	Cold air and exercise tests are both index tests – no comparator from protocol list
TERBLANCHE 1990[1722]	Wrong population: general population, not suspected asthma.
TOWNLEY1975[1762]	Not exercise test
TSYBULKINA2008[1774]	No comparator
TSYBULKINA2011[1772]	Not exercise +/- versus comparator +/-`
VILOZNI2007[1845]	Children aged 3 to 6 years (mean <5 years); not exercise test positive/

Reference	Reason for exclusion
	negative versus diagnosis or other test
VILOZNI2009[1846]	Not exercise test
WEST1996[1886]	Case control study
WOJNAROWSKI1996[1909]	Not exercise test

K.16 Monitoring: Questionnaires

Table 224: Studies excluded from the clinical review

Reference	Reason for exclusion
ADAMS 2000[16]	Validation of AQLQ-M.
APFELBACHER 2011[57]	Review article
APFELBACHER 2012[58]	Validation study of mini AQLQ-J and AQLQ-S and correlation with symptoms, control and patient characteristics.
ALMOAMARY 2012[28]	Intervention does not match protocol – asthma control questionnaire score to guide initial therapy not ongoing management.
BARLEY 1999[110]	Correlation of diary cards with questionnaires and lung function.
BATEMAN 2001[126]	Review article
BATEMAN 2006[127]	Intervention does not match protocol – step down of treatment according to monitoring using GINA guidelines.
BAYLISS 2000[133]	Validation of ITG-ASF QOL questionnaire.
BHOGAL 2006[171]	Systematic review - intervention and comparison do not match protocol – monitoring symptoms vs PEF
BIME 2012[173]	Validation study of ASUI
BRAIDO 2012[208]	Validation of RhinAsthma Patient Perspective QOL questionnaire.
BUIST 2006[243]	Intervention does not match protocol – monitoring using a peak flow monitor.
CARRANZAROSENZWEIG 2007[279]	Conference abstract
CARROLL 2013[283]	Review article
DESOUZA 2011[402]	Not in English
EHRS 2006[465]	Validation of mini AQLQ
ERKOCOGLU 2012[477]	Comparison of control determined by C-ACT or GINA
EVERHART 2009[479]	Validation of a pictorial version of the AQLQ
GALANT 1999 [534]	Conference abstract
GARRATT 2000[546]	Validation of AQLQ
GRAINGER-ROUSSEAU 1996[585]	Article not available
GREEN 2007[588]	No relevant outcomes - results of phase 2 (ACT completed for physician visits) not reported in this paper.
GREEN 2013[590]	Comparison of level of control between

Reference	Reason for exclusion
	measures (FeNO, spirometry, cACT and clinical assessment).
GUENDELMAN 2002[602]	Intervention does not match protocol – interactive self-management and education programme, includes questions about symptoms, PEF, use of medications and health services and functional status (not symptoms alone)
GUENDELMAN 2004[603]	Intervention does not match protocol – interactive self-management and education programme, includes questions about symptoms, PEF, use of medications and health services and functional status (not symptoms alone)
HALBERT 2009[620]	Systematic review of validation studies.
HOLT 2010A[685]	Review of ACT
JAN 2007[749]	Intervention does not match protocol – monitoring of symptoms and PEF (comparison of diaries and electronic diaries)
JIA 2013[769]	Systematic review of validation studies of ACT and ACQ
JUNIPER 1993[794]	Validation of AQLQ.
JUNIPER 1996[792]	Validation of PAQLQ
JUNIPER 1997[793]	Validation of the PAQLQ
JUNIPER 1999[791]	Validation of the mini AQLQ
JUNIPER 1999A[789]	Validation of the AQLQ-S
JUNIPER 1999C[797]	Validation of the ACQ
JUNIPER 2000[796]	No relevant outcomes. Comparison of daily control diary and clinician assessment of control.
JUNIPER 2001[795]	Validation of 4 QOL instruments
JUNIPER 2001A[798]	Validation of the ACQ
JUNIPER 2005[800]	Validation of the AQLQ 12+
JUNIPER 2005A[799]	Validation of 3 shortened versions of the ACQ
JUNIPER 2010[790]	Validation of ACQ in children.
KATZ 1999[821]	Validation of AQLQ-M
KAVUT 2010[826]	Intervention does not match protocol – asthma awareness session, ACT is an outcome.
KHEIR 2008[852]	Intervention does not match protocol – pharmaceutical care service including assessment of adherence and PEF monitoring to guide care plan.
KWON 2008A[941]	Conference abstract
LEUNG 2013[987]	Review article

Reference	Reason for exclusion
LIU 2007[1019]	Development and validation of cACT
LOBO 2007[1022]	Conference abstract. Validation of PAQLQ in severe asthma.
MAGNAN 2004[1048]	Review article
MARKS 1993[1078]	Validation study of AQLQ-M and correlation with symptoms, lung function and BHR.
MCDONALD 2009[1103]	Conference abstract. Validation of ACQ in children.
NATHAN 2004[1200]	Validation of the ACT
NGUYEN 2014[1216]	Validation of ACQ in children.
PINNOCK 2012[1350]	Validation of the RCP-3
PRABHAKARAN 2010A[1378]	Intervention does not match protocol - monitoring using SMS service based on symptoms and medication use.
THOMAS 2009[1729]	Validation of the RCP-3 and cross-sectional correlation analysis with control, QOL, BD use, lung function and FeNO.
TURNER 1998[1783]	Intervention does not match protocol – PEF monitoring vs symptom monitoring (symptoms monitoring does not focus on symptom scores or diaries to monitor control)
VANGAALEN 2013[1812]	Same study as MEER 2009 (included in this review). Long term follow-up at 30 months but monitoring intervention ended at 12 months. Already using outcomes at 12 months (use of 30 months would be double counting for >6months).
WING 2012[1901]	Validation of PAQLQ and mini PAQLQ.
YOOS 2002[1940]	Intervention and comparison do not match protocol – monitoring symptoms vs symptoms + PEF
ZEMEK 2008[1951]	Systematic review - intervention and comparison do not match protocol – monitoring symptoms vs PEF

K.17 Monitoring: Lung function tests

Table 225: Studies excluded from the clinical review

Study	Exclusion reason
Abramson 2010[13]	Not guideline condition. Asthma or COPD patients are included and the results are not shown separately
Abramson 2012[11]	Incorrect interventions. Spirometry intervention versus usual care (abstract only)
Anon 2004[4]	Commentary not primary study
Armour 2007[72]	Incorrect interventions. Intervention is not monitoring with spirometry or PEF
Ayres 1996[85]	Both groups monitored PEF
Berg 1997[156]	Incorrect interventions. No self-management in control group
Bheekie 2001[170]	Alternate allocation (not randomized). Inadequate allocation concealment. No relevant outcomes.
Boath 1998[181]	Conference abstract not freely available
Bramson 1996[209]	Not full paper. Commentary on a study already excluded from this review (LAHDESUO 1996)
Brouwer 2008[231]	Not SR or RCT
Charlton 1994[301]	Incorrect interventions. Both groups monitored PEF
De asis 2004[390]	No clinical outcomes. Cost-effectiveness paper based on clinical data from a paper already included in this review (COWIE 1997)
Deschildre 2012[427]	Severe asthma. Severe allergic asthma according to the Third Paediatric Asthma Consensus (i. e. frequent acute episodes requiring oral corticosteroid therapy, associated with moderate episodes (exercise-induced asthma, chronic cough, sleep disturbances, treatment with short-acting beta 2-agonists >3 times per week) and airflow limitation). Incorrect intervention. Incorrect interventions
Drummond 1994[452]	Incorrect interventions. No self-management in control group
Gibson 2002[560]	SR: self-management (PEF or symptoms) versus usual care
Gibson 2004[559]	SR: all RCTs checked
Huang 2009[709]	Not self-management in the control group
Ignacio 1993[721]	Not in English
Ignacio-garcia 1995[722]	Incorrect interventions. Intervention group received education and self-management plan. Control group were monitored by their physician according to symptoms but did not receive education or a self-mangement plan.
Jan 2007[749]	Incorrect interventions. Both groups used PEF monitoring
Janson 2010[755]	Not self-monitoring peak flow. Not self-monitoring peak flow . Not self-monitoring peak flow versus not (intervention = monthly trend PEF data given to GPs; control allowed to use PEF)
Janson-bjerklie 1988[756]	Not self-management
Jones 1995[776]	Incorrect interventions. Control group did not have self-management
Kelso 2005[837]	Commentary not primary study

Kemple 2003[839]	Action plans but not PEF monitoring versus not (not all intervention group had a peak flow monitor)
Klein 2001[875]	Control group also given peak flow meter. Incorrect interventions
Kotses 1996[908]	2 groups both self-managed with PEF, the third group did not self-manage. Incorrect interventions
Kotses 2007[909]	Conference abstract not freely available
Lahdensuo 1996[947]	Incorrect interventions. No self-management in control group
Lahdensuo 1998[946]	Incorrect interventions. Control group did not have self-management
Lefevre 2002[975]	SR: RCTs checked, all already in separately
Löwhagen 2002[1031]	Incorrect interventions. Wrong comparator (ECP)
Magar 2005[1046]	No self-management in control group
Malo 1993[1068]	Crossover study
Mcgrath 2001[1107]	SR: RCTs checked
Mcmullen 2002[1112]	Not our outcomes (qualitative data from Yoos 2002 trial)
Milenkovic 2007[1137]	Incorrect interventions. No self-management in control group
Nhlbi 2005[1217]	Protocol only, no results
Osman 2002[1274]	Incorrect interventions. No self-monitoring in control group
Persaud 1996[1325]	No self-management in control group
Powell 2002[1375]	SR: RCTs checked
Reddel 2006[1426]	Review article
Ross 2012[1469]	No self-management in control group (abstract only)
Sangha 2004[1493]	Not review population. Not persistent asthma (seasonal symptoms)
Schermer 2002[1511]	Incorrect interventions. Control group did not self-manage
Slader 2006[1605]	Incorrect interventions. Not randomised comparison of PEF monitoring versus other self-monitoring
Slader 2007[1606]	Incorrect interventions. Not randomised comparison of PEF versus symptoms monitoring
Stahlman 2006[1652]	Crossover study. Crossover
Tagaya 2005[1694]	Incorrect interventions. No self management in control group
Tapp 2007[1708]	Incorrect interventions. Education (could be self-management with PEF or symptoms or both) versus no education, not self-management with PEF versus no PEF
Thoonen 2003[1733]	Incorrect interventions. No self management in control group
Thurber 2006[1735]	Conference abstract not freely available
Toelle 2011[1747]	Withdrawn by Cochrane Library
Van der palen 1998[1805]	SR: RCTs checked
Van der palen 2001[1806]	Control group did not self-treat exacerbations
Vazquez 1993[1828]	Not PEF self-management versus other self-management. Incorrect interventions
Walders 2006[1864]	Incorrect interventions. All participants had self-management based on PEF and symptoms

Weinberger 2002[1880]	Incorrect interventions. No self-monitoring in control group
Yoon 1993[1939]	Incorrect interventions. All participants had peak flow meter; randomised comparison was of an education session
Zemek 2008[1951]	SR: all included studies already on our list individually

K.18 Monitoring: FeNO

Table 226: Studies excluded from the clinical review

Reference	Reason for exclusion
[92]BACKER 2014	Population does not match protocol. Not monitoring FeNO.
HASHIMOTO 2011[639]	Population does not match protocol – severe asthma
HONKOOP 2011[692]	Published trial protocol
HONKOOP 2013[690]	Conference abstract
KATSOULIS 2013[820]	Population does not match protocol. Not monitoring FeNO
LURA 2010[1037]	Conference abstract
MALERBA 2008[1058]	Intervention does not match protocol – monitoring FeNO and sputum eosinophils combined.
NICKELS 2014[1219]	Conference abstract
NICKELS 2014A[1220]	Conference abstract
OHKURA 2013[1262]	Conference abstract
PETSKY 2010[1337]	Conference abstract
PETSKY 2010[1336]	Conference abstract (duplicate)
PETSKY 2010[1336]	Conference abstract (duplicate)
SCHNEIDER 2014[1518]	Population does not match protocol. Not FeNO monitoring.
SYK 2012[1690]	Conference abstract
SYK 2012A[1691]	Conference abstract
VOORENDVAN 2013 [1857]	Conference abstract
VOUTILAINEN 2013[1858]	Population does not match protocol. Not FeNO monitoring.
WANICH 2009[1873]	Commentary

K.19 Monitoring: Peripheral blood eosinophils

Table 227: Studies excluded from the clinical review

Reference	Reason for exclusion
ALMOSAWI 2008[36]	Study design does not match protocol – observational case control study comparing eosinophil levels.
BASYIGIT 2004A[125]	Intervention does not match protocol – not monitoring blood eosinophils.
BELDA 2001[145]	Study design does not match protocol –

Reference	Reason for exclusion
	observational prognostic study of eosinophil levels as a risk factor for exacerbation.
BRUSSELLE 2013[238]	Review article
BUSH 2005[251]	Clinical trial protocol only. Population does not match protocol – severe asthma. Intervention does not match protocol – monitoring using sputum not blood eosinophils.
BUSSE 2013[256]	Intervention does not match protocol – not monitoring.
DEYKIN 2005[428]	Intervention does not match protocol – not monitoring.
GREEN 2002A[591]	Intervention does not match protocol (monitoring sputum eosinophils).
LOWHAGEN 2002[1031]	Intervention and comparison do not match protocol – monitoring serum eosinophil cationic protein vs monitoring PEF (as % best, not PEFv).
MALERBA 2008[1058]	Study design does not match protocol – observational case series (all patients monitored, no control group). Intervention does not match protocol (monitoring sputum eosinophils).
NIIMI 1999[1232]	Review article
PARAMESWARAN2000A[1294]	Conference abstract
PETSKY 2007[1339]	Systematic review - intervention does not match protocol (monitoring sputum eosinophils).
PETSKY 2012[1338]	Systematic review - intervention does not match protocol (monitoring sputum eosinophils).
PREHN 2000[1384]	Pilot study. Study design does not match protocol – observational case series (all patients monitored using serum eosinophil protein levels, no control group).
ZACHARASIEWICZ 2006[1946]	Review article

K.20 Monitoring: Challenge tests

Table 228: Studies excluded from the clinical review

Reference	Reason for exclusion
ARKINS 1968[70]	Not relevant to review question
BELDA 2006[146]	Intervention does not match protocol – Step-down treatment strategy, BHR as an outcome.
BRAND 1992A[211]	Population and intervention do not match protocol
FORESI 2005[503]	Intervention does not match protocol – RCT of 2 step-down treatment strategies,

Reference	Reason for exclusion
	BHR as an outcome.
HAYES 2012[644]	Intervention does not match protocol - Health Technology assessment of Mannitol challenge test for diagnosis not monitoring.
JOOS 2003A[779]	Review article
MCKINLAY 2011[1110]	Conference abstract. Relevant for mannitol
NUIJSINK 2013[1249]	Same study as NUIJSINK 2007 – long term follow up after intervention had finished.
PADOVANO 2000[1281]	Conference abstract
PROSPERINI 2002[1396]	Intervention does not match protocol – Step-down treatment strategy, BHR as an outcome.
RENSEN 1998[1435]	Conference abstract
SCHERR 2012[1513]	Conference abstract – intervention does not match protocol
SHORT 2011A[1569]	Conference abstract. Relevant for mannitol
THOONEN 2003[1733]	Intervention does not match protocol

K.21 Monitoring: Adherence to treatment

Table 229: Studies excluded from the clinical review

Reference	Reason for exclusion
APTER 2005[60]	Not full paper (clinical trial protocol only). Intervention does not match protocol.
ARMOUR 2007[72]	Intervention does not match protocol – asthma management plan including counselling/education, review of inhaler technique, review of adherence and referral to GP.
BALDWIN 1991[96]	Intervention and comparison do not match protocol – new portable system vs conventional system for monitoring theophylline levels.
BENDER 2014[152]	Conference abstract
BLACK 2008[178]	Not full paper (conference abstract only).
BOZEK 2010[207]	No relevant outcomes and does not match review question. Correlation between cognitive status and compliance in elderly people with asthma.
BRANDT 1994[217]	Intervention does not match protocol - intervention included monitoring of inhaler technique, monitoring theophylline levels and counselling. Population does not match protocol – moderate to severe asthma.
BROERS 2002[229]	Not full paper (conference abstract only).
BURGESS 2009[245]	Not full paper (conference abstract only) – full text assessed BURGESS 2010
CHIA 2008[311]	Intervention does not match protocol – education on asthma and inhaler technique.
GIBSON 2009[557]	Intervention and comparison does not match protocol – systematic review of FeNO vs symptom monitoring.
JANSON 2005[754]	Not full paper (clinical trial protocol only). Intervention does not match protocol.
KRISHNAN 2012[919]	No relevant outcomes and does not match review question – comparison between subjective and objective measures of adherence.
LAUFENBERGHORSTMANN 2006[965]	Intervention does not match protocol - community pharmacist initiated intervention included monitoring of inhaler technique and adherence.
MATUI 2014[1095]	Systematic review. Intervention does not match protocol.
MCCLURE 2008[1100]	Intervention does not match protocol - supervision of medication administration in children to improve adherence (not based on feedback as a result of monitoring

Reference	Reason for exclusion
	adherence).
MEHUYS 2008[1116]	No relevant outcomes and does not match review question. Monitoring level of asthma control to guide therapy
MITCHELL 2005[1149]	Intervention does not match protocol – asthma clinical pathway.
MOULLEC 2012[1172]	Intervention does not match protocol – systematic review of interventions to improve adherence (eg self-management and decision support).
MUNDY 2007[1178]	Review article
NIDES 1993[1225]	Population does not match protocol – not people with asthma.
PERTSEVA 2004[1327]	Not full paper (conference abstract only).
PETITTO 2012[1334]	Not full paper – full text assessed KRISHNAN 2012. No relevant outcomes and does not match review question – comparison between subjective and objective measures of adherence.
RAND 1994[1414]	Review article
SANTOS 2010[1495]	Intervention does not match protocol – counselling intervention to improve adherence.
STRANDBYGAARD 2010[1673]	Intervention does not match protocol – daily SMS reminder to take medication (adherence is an outcome, intervention is not monitoring adherence).
TRAN 2014[1763]	Systematic review. Intervention does not match protocol.
VASBINDER 2013[1827]	Intervention does not match protocol – text reminder 15 minutes following missed dose to improve adherence (not based on monitoring the individual patient's adherence)
VRIES 2010[1859]	Not in English.
VOLLMER 2011[1853]	Intervention does not match protocol – refill reminder call to improve adherence both before and after missed prescription fill (not based on monitoring the individual patient's adherence)

K.22 Monitoring: Inhaler technique

Table 230: Studies excluded from the clinical review

Reference	Reason for exclusion
BASHETI 2005[122]	No relevant outcomes – primary outcome is inhaler

Reference	Reason for exclusion
	technique score.
BASHETI 2006[121]	Conference abstract
BOSNIC 2010[197]	No relevant outcomes – primary outcome is inhaler technique score.
BRAND 2005[216]	Review article.
BYNUM 2001[258]	No relevant outcomes – primary outcome is inhaler technique score.
CICUTTO 2013[327]	Intervention does not match protocol – asthma education.
FARBER 2009[486]	Review article
GOEMAN 2013[573]	Intervention does not match protocol – asthma education.
KUETHE 2013[925]	Systematic review. Intervention does not match protocol – nurse led care vs physician led care.
KUMAR 2009[927]	Intervention does not match protocol – asthma education.
LAUFENBERGHORSTMANN 2006[965]	Study design does not match protocol – observational study.
MCELNAY 1989[1105]	Study design does not match protocol – observational study.
MULLOY 1996[1177]	Intervention does not match protocol – asthma education.
NIDES 1993[1225]	Population does not match protocol – not people with asthma.
NIMMO 1993[1234]	Population does not match protocol – asthma and COPD. Crossover study of 2 types of inhaler.
PRESS 2012[1385]	Population does not match protocol – mixed asthma and COPD (33% asthma)
ROOTMENSEN 2008[1463]	Intervention does not match protocol – asthma education.
RYDMAN 1999[1480]	No relevant outcomes – primary outcome is inhaler technique score.
SAVAGE 2003[1502]	No relevant outcomes – inhaler technique score.

Reference	Reason for exclusion
	Immediately before and after intervention, not long-term follow-up of patient outcomes.
SKAER 1996[1603]	Study design does not match protocol – observational study.
TURGEON 1996[1781]	No relevant outcomes – inhaler technique score. UHU and missed school days assessed but not reported.
VAN DER PALAN 1997[1804]	Population does not match protocol – COPD.
VERVER 1996[1838]	No relevant outcomes – inhaler technique score and self-reported symptoms.

K.23 Monitoring: Tele-healthcare

Table 231: Studies excluded from the clinical review

Reference	Reason for exclusion
ACTRN12606000400561 [80]	Abstract only (protocol or conference abstract, not a full paper)
Ahmed 2011[24]	Study protocol
Apter 2000[59]	Intervention does not match the protocol (not tele-healthcare)
Araujo 2012[61]	Study design does not match protocol (crossover design)
Arguel 2013[64]	Ongoing study
Bendeer NCT00958932[152]	Abstract only (protocol or conference abstract, not a full paper)
Burbank 2012[244]	Abstract only (protocol or conference abstract, not a full paper)
Bynum 2001[258]	Intervention does not match the protocol (not monitoring)
Chen 2013[306]	Intervention does not match the protocol (not tele-healthcare)
Clark 2007[338]	Intervention does not match the protocol (not monitoring)
Clover N0702196597 [5]	Abstract only (protocol or conference abstract, not a full paper)
Cruz-Correia 2007[376]	Study design does not match protocol (crossover design)

Reference	Reason for exclusion
De Jongste 2009[397]	Intervention does not match the protocol (FeNO monitoring)
DRKS00000584[461]	Population does not match protocol (mixed diagnoses)
Eakin 2012[463]	Intervention does not match the protocol (not tele-healthcare)
eMATIC NTR2583[1827]	Ongoing study
Finkelstein CRISP[494]	Abstract only (protocol or conference abstract, not a full paper)
Fonseca 2006[500]	Not outcome of RCT.
Friedman CRISP[2]	Abstract only (protocol or conference abstract, not a full paper)
Garbutt 2010[538]	Intervention does not match the protocol (not monitoring)
Garbutt 2012[539]	Ongoing study
Gustafson NCT00993590 [347]	Study terminated
Hashimoto 2011[639]	Population (severe asthma and monitoring to taper OCS dose)
Huang 2013[708]	Abstract only (protocol or conference abstract, not a full paper)
Ilo 2014[723]	Non-English language publication (Japanese). Education not monitoring.
Kokubu 1999[891]	Non-English language publication (Japanese)
Kokubu 2000[890]	Non-English language publication (Japanese)
Lam 2011[951]	Abstract only (protocol or conference abstract, not a full paper)
Mayers NCT00562081 [343]	Abstract only (protocol or conference abstract, not a full paper)
Merchant 2013[1123]	Abstract only (protocol or conference abstract, not a full paper)
Moldrup NCT00917410 [345]	Study design does not match protocol (no control group)
Murphy 2001[1183]	Abstract only (protocol or conference abstract, not a full paper)
NCT00149474 [340]	Abstract only (protocol or conference abstract, not a full paper)

Reference	Reason for exclusion
NCT00964301 [346]	Ongoing study
NCT01117805 [348]	Ongoing study
Osman N0411013273 [1]	Abstract only (protocol or conference abstract, not a full paper)
Partridge N0016132017 [3]	Abstract only (protocol or conference abstract, not a full paper)
Petrie 2012[1335]	No relevant outcomes (primary outcome – adherence).
Razi 2012[1425]	No relevant outcomes
Ricci 2001[1439]	Unclear methodology (could not locate any information)
Rikkers 2012[1449]	Included in monitoring questionnaires review: self-management based on monitoring online ACQ scores (no monitoring of ACQ scores in the control group)
Rikkers-Mutsaert 2010[1448]	Abstract only (protocol or conference abstract, not a full paper)
Schatz 2010[1509]	Study design does not match protocol (letter)
Sciamanna 2013[1531]	Abstract only (protocol or conference abstract, not a full paper)
Searing 2012[1537]	Abstract only (protocol or conference abstract, not a full paper)
Shanovich 2009[1554]	Abstract only (protocol or conference abstract, not a full paper)
Sparrow NCT00232557 [341]	Abstract only (protocol or conference abstract, not a full paper)
Stout 2012[1667]	Study design does not match protocol (cluster randomised feasibility trial)
Strandbygeerd 2010[1673]	No uploading of patient information.
Strunk NCT00910585[344]	Abstract only (protocol or conference abstract, not a full paper)
Taitel 2014[1697]	Not monitoring (only one telephone call)
Uysal 2013[1790]	Experimental study looking at the feasibility of using the ACT via text
van Gaalen 2012[1811]	Abstract only (protocol or

Reference	Reason for exclusion
	conference abstract, not a full paper).
VANGAALEN 2013[1812]	Included in monitoring questionnaires review: self-management based on monitoring online ACQ scores (no monitoring of ACQ scores in the control group).
Vollmer 2011[1853]	No relevant outcomes (primary outcome – adherence).
VOOREND-VAN 2013[1857]	Abstract only (protocol or conference abstract, not a full paper)
Wouters NCT00411346 [342]	Abstract only (protocol or conference abstract, not a full paper)
Yun 2013[1943]	No relevant outcomes (QOL reported incompletely, cannot combine in meta-analysis).

Appendix L: Excluded economic studies

L.1 Diagnosis: FeNO

Table 232: Studies excluded from the economic review

Reference	Reason for exclusion
BERG2008[157]	Price 2009[1387] is an update of this analysis
Harnan 2013[637]	This study only assessed diagnostic tests in isolation rather than as part of a diagnostic pathway.
PRICE2009[1387]	This study only assessed diagnostic tests in isolation rather than as part of a diagnostic pathway.

L.2 Monitoring: Lung function tests

Table 233: Studies excluded from the economic review

Reference	Reason for exclusion
De Asis[390]	This study was assessed as partially applicable with very serious limitations.

L.3 Monitoring: FeNO

Table 234: Studies excluded from the economic review

Reference	Reason for exclusion
Price 2009[1387]	This study was assessed as partially applicable with very serious limitations. Harnan et al. 2013[637] is more recent and more applicable.
Berg 2008[157]	This study was assessed as partially applicable with very serious limitations. Price et al. 2009[1387] updated this analysis using a UK NHS perspective and is hence more applicable.

L.4 Monitoring: Tele-healthcare

Table 235: Studies excluded from the economic review

Reference	Reason for exclusion
Pinnock 2007[1347]	Only includes cost to the service rather than cost to the NHS. Including these additional costs could change the results of the study as cost differences are very small.
Pinnock 2005[1349]	Only uses proportion of patients reviewed as an outcome. Excluding quality of life from the analysis could change the results as face to face reviews may improve health outcomes.

Appendix M: Cost-effectiveness analysis: Diagnosis of asthma in adults and young people aged over 16

M.1 Introduction

There are a variety of tests that can be used to diagnose asthma, and no clear gold standard. Available tests have different costs and different levels of accuracy, therefore it is important to identify which combination of tests represents a cost-effective use of NHS resources. Currently it is believed that asthma is over-diagnosed with a large portion of individuals with asthma currently being in-correctly diagnosed. This concern has been confirmed in a recent study by Aaron et al[6] which found that nearly a third of individuals with an asthma diagnosis did not have asthma. Misdiagnosis of asthma represents a large waste of NHS resources as a significant portion of patients will be receiving treatment that does not improve their condition. For these reasons the GC prioritised original economic analysis to be conducted to compare different combinations of diagnostic tests for the diagnosis of asthma. This analysis will weigh up the cost of providing additional tests against the cost savings from reducing unnecessary asthma treatment and improved health outcomes from providing the correct treatment.

The economic review found no studies that assessed the cost-effectiveness of diagnostic pathways. However two studies were found which assessed the cost-effectiveness of asthma diagnostic tests as standalone tests. Although the results from these studies give little indication of how cost-effective a test will be as part of a pathway they do give insight into the methods used to build an economic model for asthma diagnosis. These methods are compared to the following analysis in M.4.4.

M.2 Methods

M.2.1 Model overview

M.2.1.1 Comparators

Six diagnostic strategies were created using combinations of the following tests:

- spirometry
- bronchodilator reversibility
- FeNO
- peak expiratory flow variability
- challenge tests.

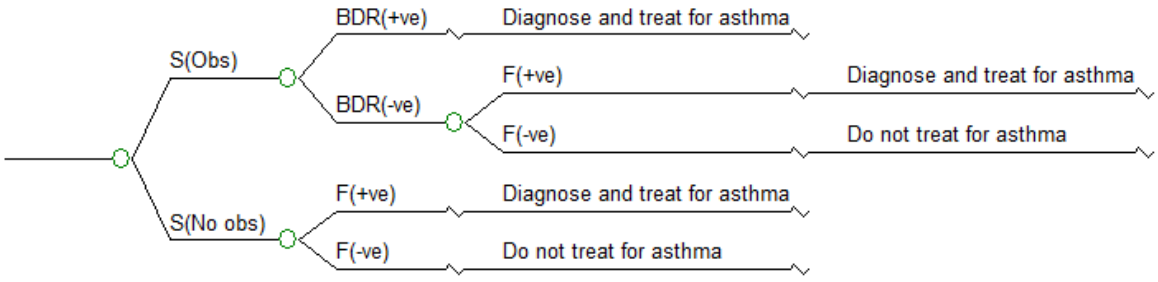
When comprising the diagnostic algorithms the GC considered the diagnostic accuracy of the test alongside the practicality of performing the test. The GC agreed that spirometry should be conducted first as the results can be reported straight away, unlike PEFv whereby monitoring takes place over two weeks, and the test is fairly common and well used in practice. The results can also help rule-out other conditions such as COPD and can be followed up immediately with a bronchodilator reversibility (BDR) test. After a BDR test the GC agreed that FeNO would be the next most sensible test to conduct as combined with

previous results from the spirometry and BDR test the clinician would have a very good indication as to whether the individual had asthma. After FeNO, where appropriate, PEFv would be the next logical test to conduct as the diagnosis can be kept in primary care. If the diagnosis remains uncertain after the results from these tests then the GC agreed the individual should be referred for a challenge test, which is performed outside of primary care.The GC agreed that only one challenge test would ever be conducted per patient meaning that challenge testing would only appear once in a diagnostic strategy. Therefore once the diagnostic strategies were developed it was proposed to duplicate each strategy which used challenge testing using the diagnostic accuracies and costs of histamine/methacholine, mannitol or exercise challenge test. However once the costs of an exercise challenge test and a methacholine challenge test had been established it was apparent that the exercise challenge test was the more expensive test (see M.2.3.7). The clinical review also found that exercise challenge tests had a lower sensitivity and specificity when compared to a methacholine challenge test. Therefore exercise challenge tests were not modelled as they would always be dominated (more costly and provide lower health outcomes) when compared to methacholine challenge tests. Mannitol was also not modelled as the clinical review found it had a low sensitivity and specificity. Adding mannitol to the diagnostic pathway would in fact decrease the overall diagnostic accuracy of the pathway making it dominated by strategies that did not use challenge tests.

Strategy 1

Strategy 1 involves the fewest number of tests. The exact point that each test appears in the diagnostic pathway and at which point patients are diagnosed with asthma is shown in Figure 306. For example in Figure 306 spirometry (S) is used as the initial test, followed by bronchodilator reversibility (BDR) if S detects obstruction (Obs) or FeNO (F) if S does not detect obstruction (No obs). BDR is not performed after a non-obstructive spirometry as there is no obstructive airway to reverse. If BDR is negative this is followed by F. A diagnosis of asthma is made with either a positive BDR or F, while asthma is excluded only with a negative F.

Figure 306: Strategy 1



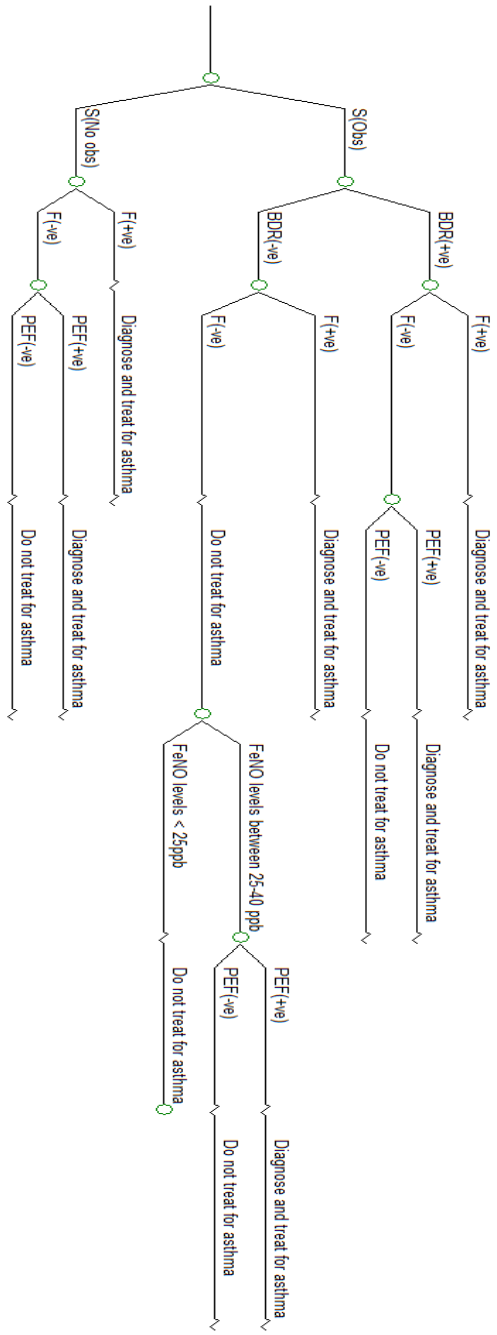
(-ve): negative; (+ve): positive; BDR: bronchodilator reversibility test; F: FeNO; S: spirometry; (Obs): obstruction

Strategy 2

The second strategy involves spirometry, bronchodilator reversibility, FeNO and PEF variability (PEF). The diagnostic pathway is shown in Figure 307. As more tests can be conducted after a FeNO test, if a patient receives a negative FeNO test, the FeNO level that

was measured in the patient is also taken into account when deciding what to do next. This test is considered negative when the FeNO level is below 40 parts per billion (ppb), however the confidence in excluding a diagnosis of asthma depends on how close to this cut off the result is. If the FeNO level is below 25 parts per billion (ppb), along with an obstructive spirometry and a negative BDR, asthma is ruled out. If the FeNO level is between 25 – 40ppb then the diagnosis of asthma still cannot be ruled out and further tests are conducted. In strategy 2 below the patient goes on to have a PEFv test.

Figure 307: Strategy 2

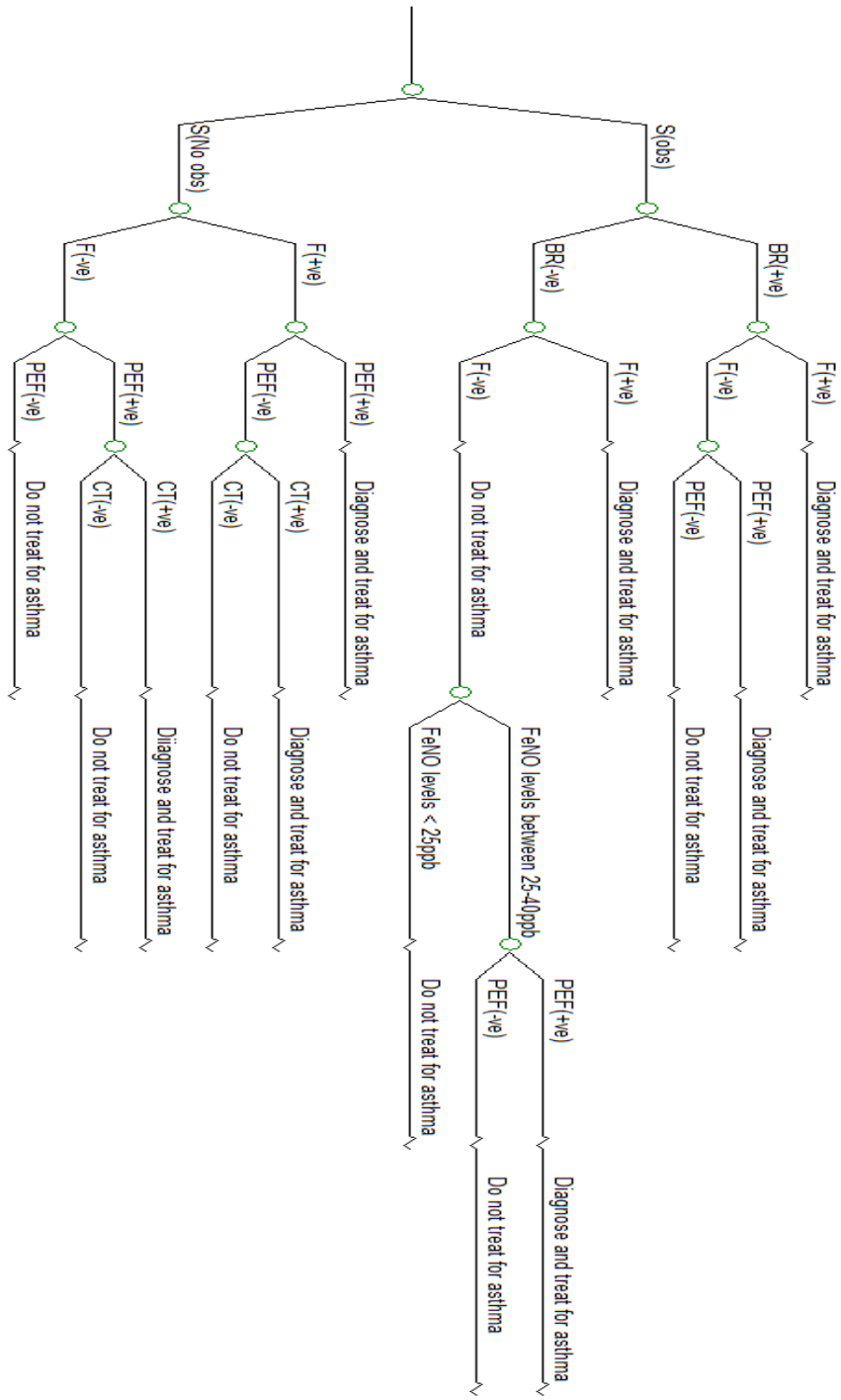


(-ve): negative; (+ve): positive; BDR: bronchodilator reversibility test; F: FeNO; S: spirometry; (Obs): obstruction; PEF: peak expiratory flow variability

Strategy 3

The third strategy uses spirometry, bronchodilator reversibility, FeNO, PEF variability and a methacholine challenge test (CT). The diagnostic pathway is shown in Figure 308. Note in this pathway challenge tests are only used on patients who have a non-obstructive spirometry.

Figure 308: Strategy 3

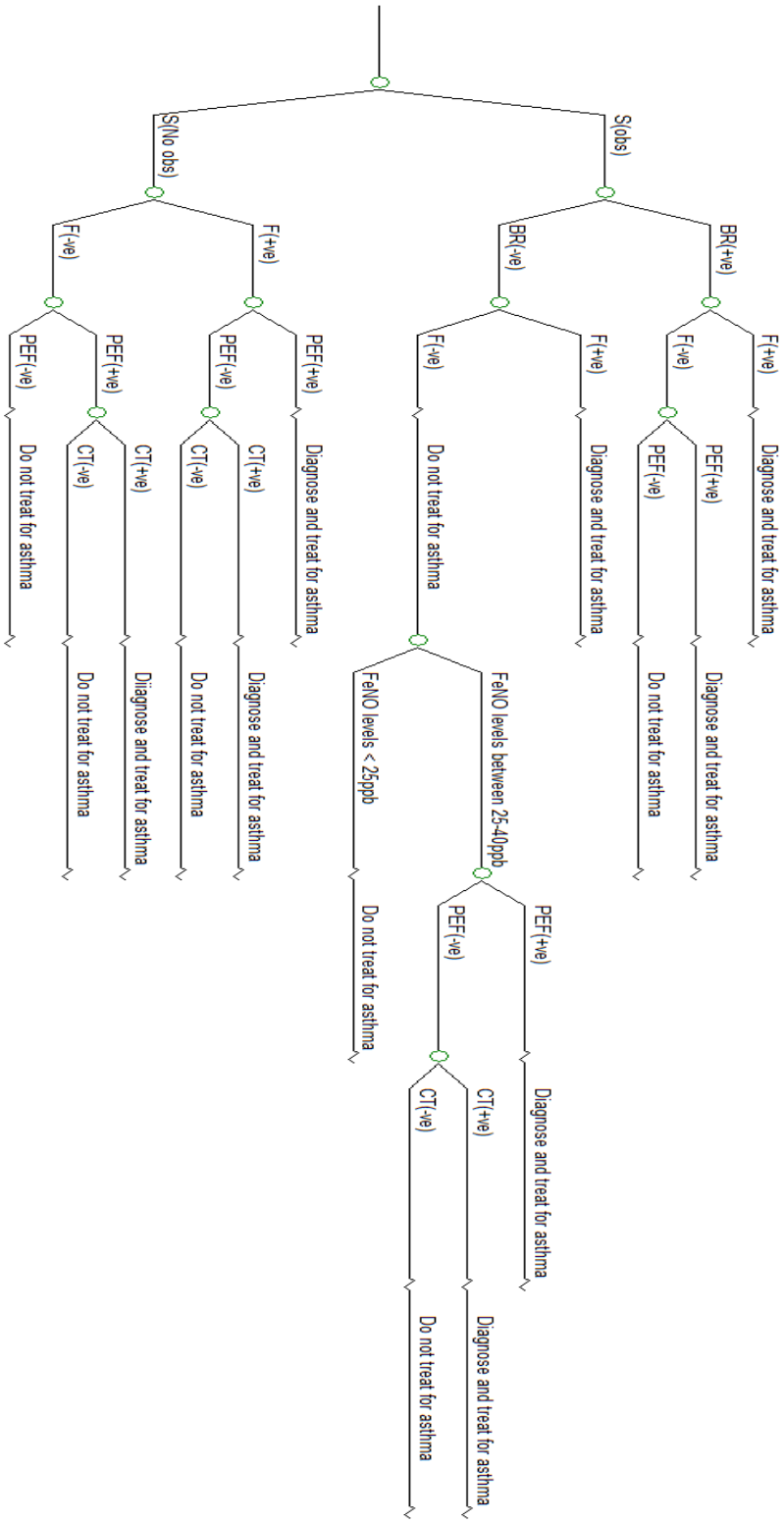


(-ve): negative; (+ve): positive; BDR: bronchodilator reversibility test; CT: challenge test; F: FeNO; S: spirometry; (Obs): obstruction; PEF: peak expiratory flow variability

Strategy 4

The forth strategy shown in Figure 309 expands the use of challenge tests as seen in strategy 3. Now a CT is also conducted on patients with a positive BDR, negative FeNO and a negative PEFv result. The use of FeNO levels is also taken into account, whereby a CT is only conducted in this arm when FeNO levels are between 25-40ppb.

Figure 309: Strategy 4

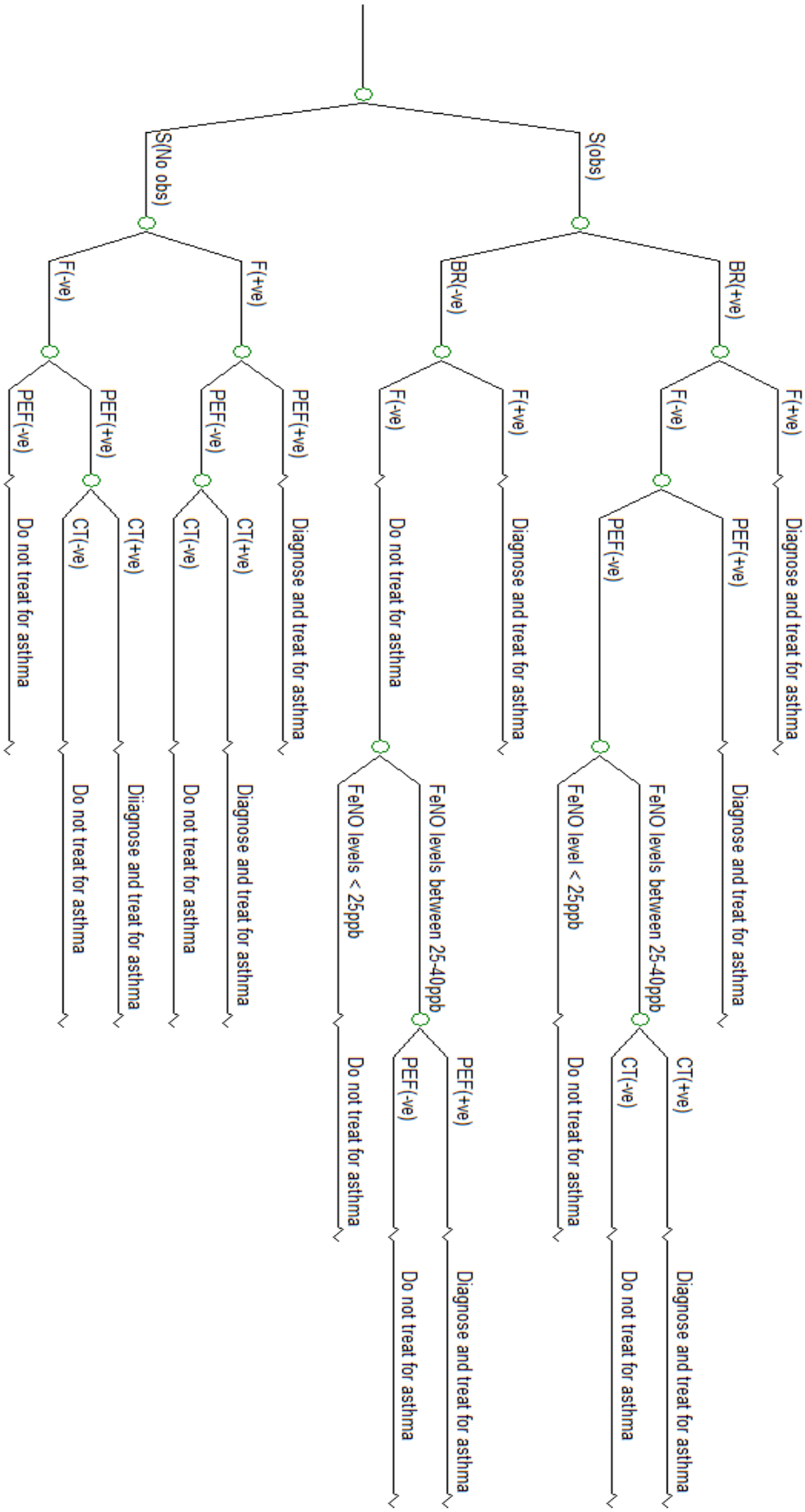


(-ve): negative; (+ve): positive; BDR: bronchodilator reversibility test; CT: challenge test; F: FeNO; S: spirometry; (Obs): obstruction; PEF: peak expiratory flow variability

Strategy 5

The fifth strategy, shown below in Figure **310**, also expands the use of challenge tests, as seen in strategy 3, however places the additional CT at a different point in the pathway. Now a CT is also conducted on patients with a negative BDR, negative FeNO (between 25-40ppb) and a negative PEFv test result.

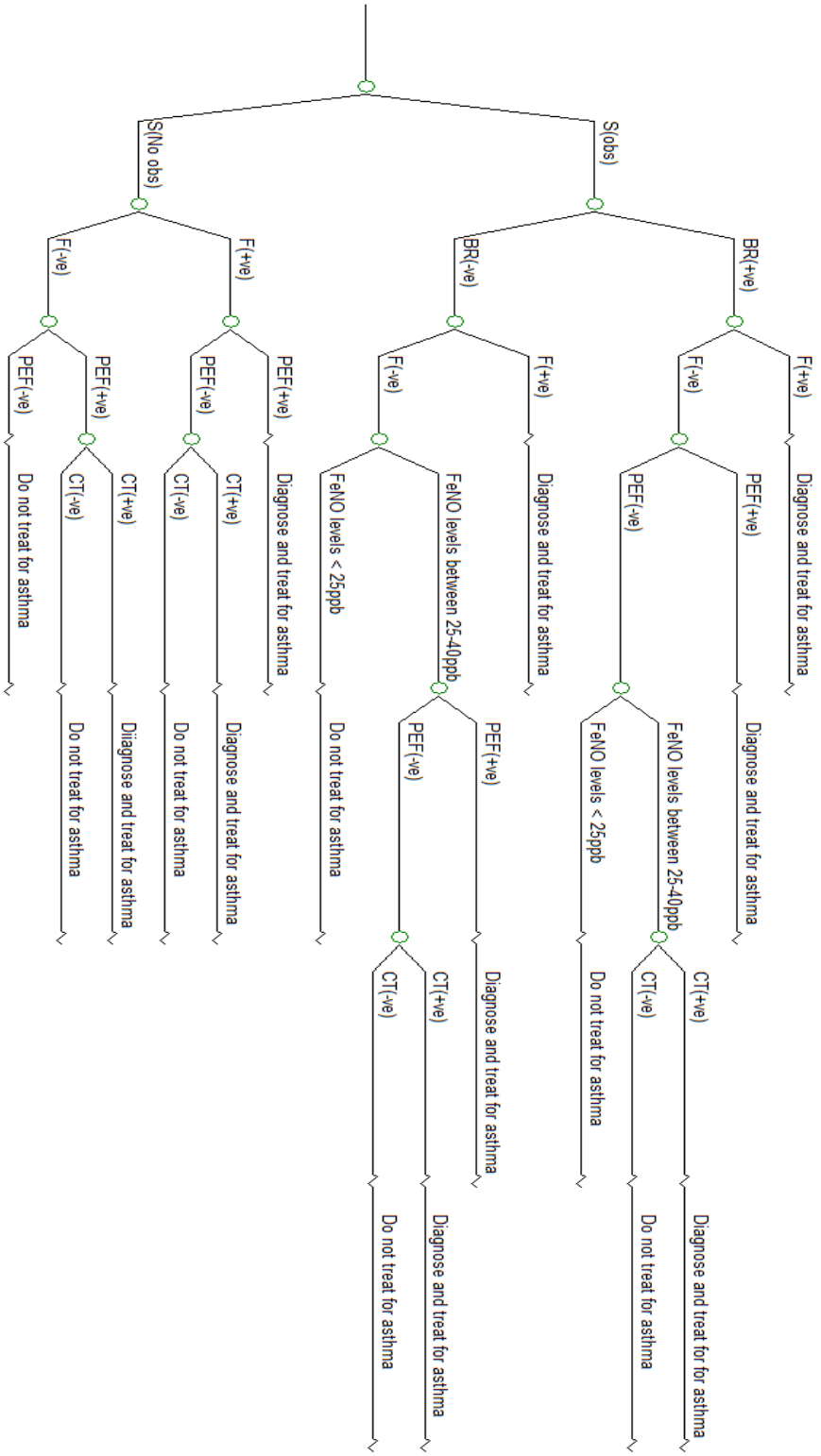
Figure 310: **Strategy 5**



Strategy 6

The sixth strategy, shown below in Figure 311, is the most comprehensive and uses the maximum number of challenge tests.

Figure 311: Strategy 6



Strategy 7

A final strategy considered involves not giving the patient any tests and diagnosing without the use of objective tests. To make this strategy more reflective of current practice it is assumed that some of the non-asthmatics will be correctly diagnosed as not having asthma. One prevailing thought is that one third of people currently diagnosed with asthma are misdiagnosed, ie they do not have asthma (False positive) according to a study by Aaron et al[6]. Therefore the proportion of false positives calculated in this strategy will be a third of the total number of positive diagnoses made:

$$\frac{False\ positives}{False\ positives + True\ positives} = \frac{1}{3}$$

As no tests are conducted the only costs that are incurred in this strategy are those that occur after the diagnosis is made (e.g. the cost of asthma treatment). An assumption was made that all people with asthma are correctly diagnosed giving this strategy a sensitivity of 100%.

M.2.1.2 Population

The model considers patients over 16 years of age who present symptoms of asthma to their GP. Patients who present symptoms in a secondary care setting are not considered.

A separate analysis was considered for children between 5 – 16 years of age. However there were no included studies in the clinical review which identified the diagnostic accuracy of bronchodilator reversibility in this age group. As this test would appear in all diagnostic pathways its diagnostic accuracy would highly influence which pathway is cost-effective. On top of this, the evidence found for the diagnostic accuracies of other tests on children was weak.

M.2.1.3 Time horizon, perspective, discount rates used

The analysis follows the standard assumptions of the reference case including discounting at 3.5% for costs and health effects, and incremental analysis is conducted. A sensitivity analysis using a discount rate of 1.5% for costs and 1.5% for health benefits is conducted. A lifetime horizon has been chosen to fully capture the long-term adverse outcome derived from incorrect diagnosis.

M.2.2 Approach to modelling

The model is based on two parts:

- **Decision tree** - Using the sensitivity and specificity, combined with data on the prevalence of asthma in the defined population, the model identifies the proportion of patients that receive a true positive (TP), true negative (TN), false positive (FP) or false negative (FN) diagnosis.
- **Markov model** - Once the diagnosis is made the patient moves on to the second part of the model which involves a Markov model to fully evaluate the patients' health and cost outcomes.

Further information and technical details are provided below.

M.2.2.1 Model structure

Diagnostic pathways (decision tree)

First of all patients go through a decision tree to calculate the proportion that will receive either a FN, FP, TN or TP diagnosis. The way this is calculated is shown below in Figure 309. Here strategy 1 is used as an example (detailed in **Figure 306** above).

In Figure 309 below the circles represent chance nodes. This means that the outcome is determined by a probability, rather than a decision. When the patient enters the model, they have a probability of having asthma or not, depending on the asthma prevalence in the defined population. If the patient has asthma then the probability of a test result being positive is determined by the sensitivity of that test. If the patient does not have asthma then the probability of the test result being negative is determined by the specificity of that test. Using these probabilities the decision tree can calculate the proportion of patients that will end up at each arm. For example the probability of an asthmatic patient having an obstructive spirometry and a positive result from a bronchodilator reversibility test is:

$$Probability\big(Asthma \cap S(Obs) \cap BDR(+ve)\big) = (Probability\ of\ having\ asthma) * (Sensitivity\ of\ spirometry) * (Sensitivity\ of\ bronchodilator\ reversibility)$$

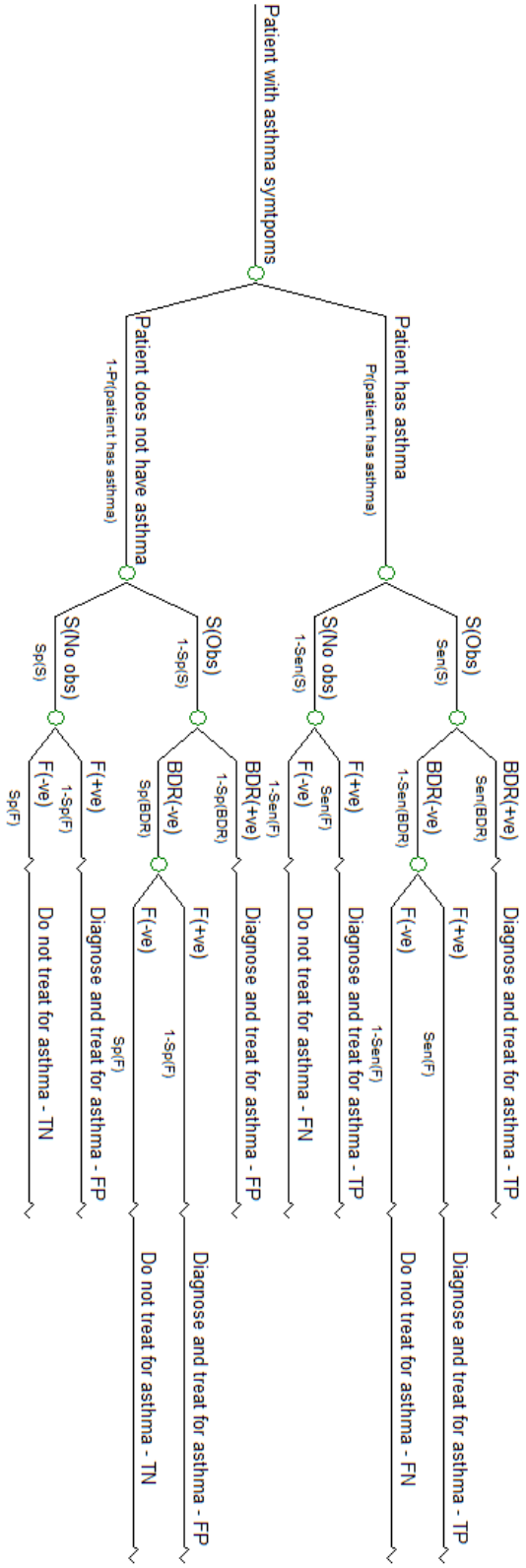
In this case the patient will receive a true positive diagnosis. Likewise the probability of a non-asthmatic having an obstructive spirometry and a positive BDR result is:

$$Probability\big(No\ Asthma \cap S(Obs) \cap BDR(+ve)\big) = (Probability\ of\ not\ having\ asthma) * (1 - Specificity\ of\ spirometry) * (1 - specificity\ of\ bronchodilator\ reversibility)$$

In this case the patient will receive a false positive diagnosis.

Once the proportion of patients that will receive either a TP, TN, FP or FN diagnosis is calculated, final health and cost outcomes are determined by a Markov model which is discussed below.

Figure 312: Calculating patient movement through the model



(-ve): negative; (+ve): positive; BDR: bronchodilator reversibility test;; F: FeNO; S: spirometry; (Obs): obstruction; Sen: sensitivity; Sp: specificity; TP: True positive; FP: false positive; FN: False negative; TN: True negative.

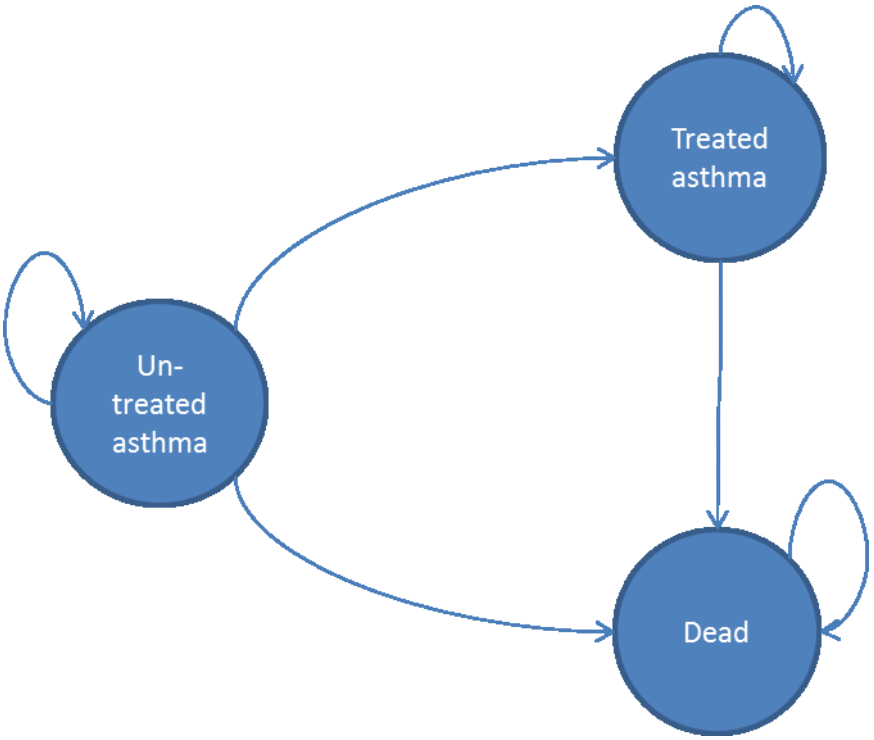
Calculating health and cost outcomes after diagnosis for patients who have asthma (Markov model)

The decision tree will determine the proportion of people with asthma that receive a correct diagnosis (true positive) and that receive an incorrect diagnosis (false negative).

False negatives

After a false negative diagnosis is made the patient enters the Markov model depicted in Figure 313.

Figure 313: Markov model for false negative diagnoses



The patient starts in the state 'un-treated asthma'. After a cycle length of six months there is a probability that the false negative diagnosis will be rectified and the patient will be treated for asthma. This probability is determined by whether or not the patient has an exacerbation. It is assumed that after an exacerbation the patient will be correctly re-diagnosed as having asthma. In this case the patient is treated and moves from 'un-treated asthma' to 'treated asthma'. After one year has passed the patient will move to treated asthma, regardless of whether they have had an exacerbation, and a re-diagnosis cost is added. This is to reflect that a patient with un-treated asthma will have persisting symptoms and an assumption was imposed that a methacholine challenge test along with a respiratory outpatient visit and persisting asthmatic symptoms would guarantee a correct diagnosis at this point. The probability of the patient entering the dead state is contingent on an all-cause mortality rate plus an added mortality risk associated with an exacerbation. As the patient is more likely to exacerbate if they are untreated, the mortality risk is slightly higher for un-treated asthmatics.

The costs associated with each state are discussed in section M.2.3.7. The quality of life (QoL) associated with each state is discussed in section M.2.3.6.

True positives

After a true positive diagnosis is made the patient enters the Markov model depicted in Figure 314.

Figure 314: Markov model for true positive

The patient starts in the 'treated asthma' state and remains there until they die. The QoL, exacerbations, and costs associated with this state are the same as those in the 'treated asthma' state in Figure 313.

Calculating health and cost outcomes after diagnosis for patients that do not have asthma (Markov model)

The decision tree will determine the proportion of non-asthmatic patients that receive a correct diagnosis (true negative) and the proportion that receive an incorrect diagnosis (false positive).

An important aspect of the model was to consider the condition the individual is likely to have if they present asthma symptoms but don't have asthma. The true underlying condition the patient has will determine the length and severity of misdiagnosis. The GC identified four sub-groups of patients that would have asthmatic symptoms but not have asthma:

The first two subgroups of patients would have an illness that would go un-treated if an asthma diagnosis were made, as the physician would believe the patient was being correctly treated. As these patients would forego correct treatment then during this period of incorrect diagnosis they would receive a lower quality of life, relative to what they could achieve with optimal treatment. The NHS would also incur unnecessary asthma treatment costs. The GC considered that the two main groups this would affect are patients with COPD or chronic heart failure. As these patients will remain symptomatic after asthma treatment the probability of re-diagnosis will be high and increase over time as it becomes clearer that asthma treatment is not helping the patients. It is worth noting that once these patients are being correctly treated the NHS will now incur the cost of the respective treatment meaning that re-diagnosis is not necessarily cost-saving.

The third and fourth subgroups of patients would not forego any treatment because they are labelled as having asthma. Therefore for these patients there is no disutility from being labelled as asthmatic; instead the only disadvantage of incorrect diagnosis is that the NHS has to incur unnecessary asthma treatment costs. The GC considered that the two main groups this would affect are patients with physical de-conditioning or short-lived acute symptoms. Patients with short-lived acute symptoms, such as those recovering from an infection, would not be on asthma medication long as they would quickly become asymptomatic, naturally rather than due to medication, and stop taking asthma medication.

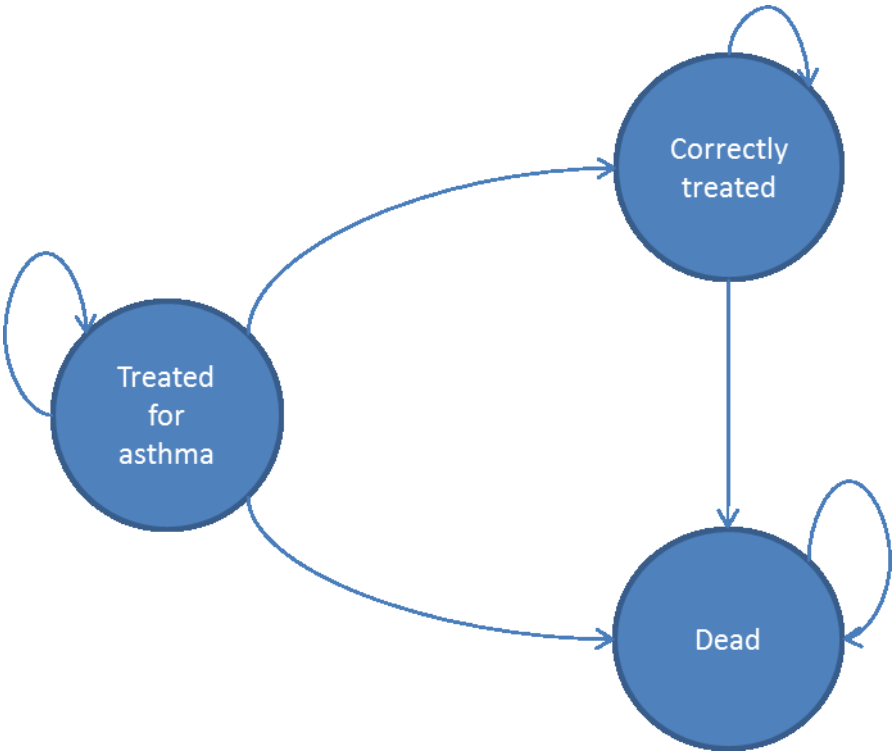
Individuals with physical de-conditioning however could remain on asthma medication for a long time as they remain symptomatic but symptoms would rise and fall over time.

The GC recognised that there would be other conditions that the patient could have however the four outlined above would cover the majority and those not covered would produce similar outcomes to those outlined above. As there is no data in the literature on the distribution of diseases amongst the misdiagnosed asthmatics an assumption was made that the probability of a patient having one of the above conditions was equal. This assumption, along with all data inputs used for these patients, are extensively tested in the sensitivity analysis, detailed in section M.2.5.

False positives

After a false positive diagnosis is made the patient enters the Markov model depicted below in Figure 315.

Figure 315: Markov model for false positives



The individual starts in the state 'treated for asthma', as the individual does not have asthma this can be classed as 'incorrect treatment'. After a cycle length of six months there is a probability that the individual will be correctly diagnosed as not having asthma. This probability is contingent on the under-lying condition the individual has. After each cycle the probability of correct diagnosis increases, the extent to which also depends on the patient's underlying condition. This is to reflect the fact that the longer un-treated symptoms reside the more likely the physician is to make a re-diagnosis. If the individual is correctly re-diagnosed then they move to the state 'correctly treated', which means they are receiving the treatment for the condition they actually have (if a treatment is required), where they remain until they die. The model assumes that once asthma is excluded, the real condition is diagnosed correctly. To enter the state 'correctly treated' it is assumed that a patient has a respiratory outpatient visit and under-goes a methacholine challenge test to rule-out the diagnosis of asthma, as this test was identified as having the highest sensitivity and

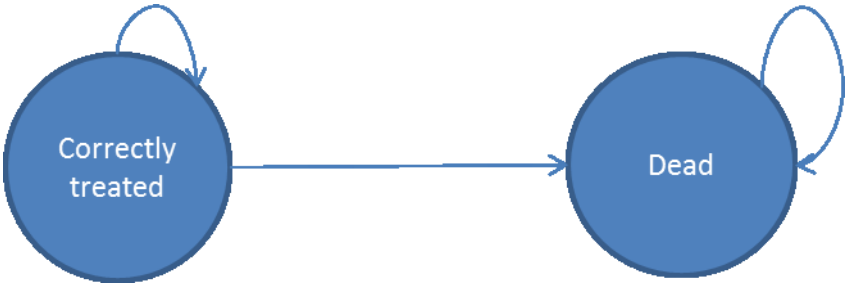
specificity in the clinical review. A sensitivity analysis was conducted around re-diagnosis costs as detailed in section M.2.5.

The costs associated with each state are discussed in section M.2.3.7. The quality of life (QoL) associated with each state is discussed in section M.2.3.6.

True negatives

After a true negative diagnosis is made the patient enters the Markov model in Figure 316.

Figure 316: Markov model for true negative



It is assumed that by ruling out asthma as a potential cause of symptoms the individual will start in the state 'correctly treated', which means they are receiving the treatment for the condition they actually have (if a treatment is required) and remain there until they die. The QoL and costs associated with this state are the same as those in Figure 315.

M.2.2.2 Key assumptions

The key assumptions of the model are summarised in **Table 236** below:

Table 236: Summary of key assumptions

Assumption	Comment
A patient with a false negative diagnosis will always be correctly re-diagnosed after an exacerbation.	
A patient with a false negative diagnosis will remain misdiagnosed for a maximum of one year, even if an exacerbation does not occur.	
Adults correctly identified as not having asthma will either have, with equal probability: acute symptoms, physical de-conditioning, chronic heart failure or COPD.	This assumption was built into the model to address the concern that those identified as not having asthma are likely to have something else. This ensures the model gives a better reflection of the true costs and health losses incurred through misdiagnosis.
After a true negative diagnosis patients are assumed to be correctly treated for their true underlying condition.	This assumption is built on the fact that ruling out asthma as a potential cause of symptoms will help rule in the true diagnosis after further tests. The costs of these tests (such as an echocardiogram) have been excluded from the model as they will be incurred for both true negatives and false positives and therefore there will be no incremental cost.
Uncontrolled asthma was used as a proxy for	

Assumption	Comment
untreated asthma when calculating QoL	
FeNO is conditionally independent with other tests	As FeNO is the only test in the model that measures inflammation of the airways a patient's FeNO count is unlikely to be dependent on the results of other tests. Likewise other lung function test results are unlikely to be dependent on a patient's FeNO count. Therefore this test was considered to be conditionally independent with all other tests. Further details regarding conditional independence are provided in section M.2.2.3 below.

M.2.2.3 Conditional dependence

In the clinical review, the sensitivity and specificity of each test was calculated across the whole population of interest. However, if a test is only conducted after a certain test result (for example if test 2 is only conducted following a positive result from test 1 then ideally we would use accuracy data for the second test on this sub-group of the original population. The sensitivity and specificity of a test will be different in this sub-group if the two tests (T1 and T2 in example below) are conditionally dependent. **Table 237** below shows how conditional dependence affects the probability of obtaining two test results.

Table 237: Probability of obtaining two test results

Event	Probability
Patients who have the disease	
T1(+ve) AND T2(-ve)	$Se(T1) \times (1 - Se(T2)) - \gamma_{se}$
T1(+ve) AND T2(+ve)	$Se(T1) \times Se(T2) + \gamma_{se}$
T1(-ve) AND T2(+ve)	$(1 - Se(T1)) \times Se(T2) - \gamma_{se}$
T1(-ve) AND T2(-ve)	$(1 - Se(T1)) \times (1 - Se(T2)) + \gamma_{se}$
Patients who do not have the disease	
T1(+ve) AND T2(-ve)	$(1 - Sp(T1)) \times Sp(T2) - \gamma_{sp}$
T1(+ve) AND T2(+ve)	$(1 - Sp(T1)) \times (1 - Sp(T2)) + \gamma_{sp}$
T1(-ve) AND T2(+ve)	$Sp(T1) \times (1 - Sp(T2)) - \gamma_{sp}$
T1(-ve) AND T2(-ve)	$Sp(T1) \times Sp(T2) + \gamma_{sp}$

Abbreviations: Se = sensitivity; Sp = specificity; T1 = test 1; T2 = test 2; γ_{se} = sensitivity covariance; γ_{sp}= specificity covariance

From **Table 237** shows that the probability of obtaining any one result is dependent on the covariance between the two sensitivities γ_{se} or specificities γ_{sp}. Assuming that tests 1 and 2 are positively correlated, the upper-limit of these co-variances can be calculated as follows:

$$\gamma_{se} = MIN(Se_1(1 - Se_2); Se_2(1 - Se_1))$$

$$\gamma_{sp} = MIN(Sp_1(1 - Sp_2); Sp_2(1 - Sp_1))$$

where MIN is a function which selects the minimum value between those listed.

This limit ensures the probability of obtaining two test results is bounded between zero and one. Therefore the covariance must fall between zero and this upper limit. If a test result is highly dependent on a previous test result then the covariance is likely to fall closer to the upper limit. If the result of the second test is fairly independent from the result of the first

test then the covariance will be closer to zero. This method is outlined in full in Gardener et al[545].

For the model the GC were asked to give their opinion on how strongly they believed the conditional dependence between two tests were. Tests that were weakly dependent were given a covariance value closer to zero; tests that were moderately dependent were given a value midway between zero and the upper limit. The results are shown in **Table 238**. Some points to note:

- FeNO does not appear as it was assumed to be conditionally independent with the other tests.
- The diagnostic review on bronchodilator reversibility was assessed in patients that had an obstructive spirometry therefore conditional dependence will have already been taken into account between those two tests.
- The conditional dependence between spirometry and other tests has not been considered as the GC agreed that other test results are unlikely to be dependent on the results from a single spirometry.
- Finally it is assumed that the dependence between tests will be the same for individuals with and without asthma. Therefore the strength of dependence applies equally to specificities and sensitivities.

Table 238: Strength of dependence between tests

Test 1	Test 2	Strength of dependence (value given between 0 and 1)	Source
Bronchodilator reversibility	PEFv	Weak (0.1)	GC opinion
PEFv	Histamine/Methacholine	Moderate (0.5)	GC opinion
Bronchodilator reversibility	Histamine/Methacholine	Moderate (0.5)	GC opinion

Abbreviations: PEFv= Peak expiratory flow variability

Using this information and the formulas in **Table 237** the sensitivity and specificity of tests which occur further down the pathway can be re-calculated to account for conditional dependence. For example the specificity of test 2 for patients without asthma who test positive for test 1 is:

$$Sp_2 = \frac{\text{Probability}(T1_{+ve} \cap T2_{-ve})}{Sp_1}$$

Using the formula for $\text{Probability}(T1_{+ve} \cap T2_{-ve})$ from **Table 237** and results from **Table 238** we know:

$$\text{Probability}(T1_{+ve} \cap T2_{-ve}) = (1 - Sp_1)(Sp_2) - \{(\gamma_{sp}) * (Strength\ of\ dependence)\}$$

Here 'strength of dependence' lies between zero and one.

Although conditional dependence has been incorporated into the model not every dependency has been accounted for. As challenge tests are incorporated last in the diagnostic pathway they will have the most dependencies between tests. In the model conditional dependence has not been fully incorporated for challenge test results that are dependent on more than one test result. In some circumstances a challenge test will be dependent on the results from a PEFv test and a BDR test. An assumption was made that if a

challenge test proceeds a BDR and PEFv test then the conditional dependence will only be taken into account between the BDR test and the challenge test. Rather than formally model three way dependencies, this issue has been examined in a sensitivity analysis detailed in section M.2.5.

M.2.2.4 Uncertainty

The model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run 5,000 times for the base case.

Table 239: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution
Specificity	Beta	Bounded between 0 and 1. As the sample size and the number of events were specified r and n values were calculated as follows: r=(True negatives) n=(Number of patients)-(True negatives)
Diagnostic Odds ratio (DOR)[a]	Normal	Derived from: Mean = ln(DOR) Standard error = Se(ln(DOR))
Exacerbation rate	Log-normal	Derived from the mean and standard deviation
Utility , asthma prevalence, transition probabilities, covariance strength	Beta	Bounded between 0 and 1. Derived from mean of a domain and its standard error, using the method of moments. Alpha and beta values were calculated as follows: $Alpha = mean^2 *[(1-mean)/SE^2]-mean$ $Beta = Alpha*[(1-mean)/mean]$
NHS Reference Costs, test costs	Gamma	Bounded at 0, positively skewed. Derived from mean and its standard error. Alpha and lambda values were calculated as follows: $Alpha = (mean/SE)^2$ $Lambda = SE^2/Mean$

Note: When the standard error (SE) is not given an assumption was imposed that the SE is 20% of the mean.
a) The use of the diagnostic odds ratio is discussed in section M.2.3.3

In addition, various deterministic sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change.

As sensitivities were estimated as functions of other variables, no distributions were attached to these parameters.

M.2.3 Model inputs

M.2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated with clinical members of the GC. A summary of the model inputs used in the base-case (primary) analysis is provided in Table 240 below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 240: Summary of base-case model inputs

Input	Input	Source
Probability patient is male (adult)	0.40	Weighted average from the diagnostic studies identified in the clinical review
Patient age at diagnosis (adult)	43	Weighted average from the diagnostic studies identified in the clinical review
Time horizon	Lifetime	
Discount rate	Costs = 3.5%; effects = 3.5%	

Table 241: Overview of parameters and parameter distributions used in the model

Parameter description	Point estimate	Probability distribution	Distribution parameters	Source
Decision tree probabilities				
Prevalence of asthma	0.406	Beta	$\alpha = 606, \beta = 887$	*Taken from a meta-analysis of the diagnostic studies identified in the clinical review, see section (A.2.3.2)*
Sensitivity of spirometry	0.465	-	-	Pino 1996[1351]
Specificity of spirometry	0.415	Beta	r = 17, n =41	Pino 1996[1351]
Ln(Diagnostic odds ratio for spirometry)	-0.485	Normal	$\mu = -0.485, \sigma = 0.44$	*Derived from sensitivity and specificity, see section M.2.3.3*
Sensitivity of BDR used in model	0.409	*Distributions were fitted directly on the parameters derived from each of the two studies and in each iteration the pooled average was calculated from the individual parameters.*	-	Pooled average from Kim 2012[861] and Chhabra 2005[310] below
Specificity of BDR used in model	0.713		-	Pooled average from Kim 2012[861] and Chhabra 2005[310] below - see below

Parameter description	Point estimate	Probability distribution	Distribution parameters	Source
Sensitivity of BDR (Chabbra 2012)	0.65	-	-	Chhabra 2005[310]
Specificity of BDR (Chabbra 2012)	0.811	Beta	r = 125, n =154	Chhabra 2005[310]
Ln(Diagnostic odds ratio for BDR) (Chabbra 2012)	2.08	Normal	μ = 2.08, σ = 0.25	Derived from sensitivity and specificity, *section M.2.3.3*
Sensitivity of BDR (Kim 2012)	0.168	-	-	Kim 2012[861]
Specificity of BDR (Kim 2012)	0.614	Beta	r = 89, n =145	Kim 2012[861]
Ln(Diagnostic odds ratio for BDR) (Kim 2012)	-1.14	Normal	μ = -1.14, σ = 0.22	*Derived from sensitivity and specificity, section M.2.3.3*
Sensitivity of FeNO	0.88	-	-	Kowal 2009[914]
Specificity of FeNO	0.83	Beta	R = 299, n =362	Kowal 2009[914]
Ln(Diagnostic odds ratio for FeNO)	3.57	Normal	μ =3.57 , σ = 0.27	*Derived from sensitivity and specificity, section M.2.3.3*
Sensitivity of PEFv	0.116	-	-	Thiadens 1998[1727]
Specificity of PEFv	0.99	Beta	R = 100, n = 101	Thiadens 1998[1727]
Ln(Diagnostic odds ratio for PEFv)	2.57	Normal	μ = 2.57, σ = 1.07	*Derived from sensitivity and specificity, section M.2.3.3*
Sensitivity of histamine challenge test	0.933	-	-	Kowal 2009[914]
Specificity of histamine challenge test	0.99[(a)]	Beta[(a)]	R = 358, n =362	Kowal 2009[914]
Ln(Diagnostic odds ratio for histamine challenge test)	8.52	Normal	μ =8.52 , σ = 1.05	*Derived from sensitivity and specificity, section M.2.3.3*
Mean FeNO level for an asthmatic	96	Lognormal	μ = 4.32, σ = 0.52	*See section M.2.3.3 for derivation*
Probability that FeNO level < 25ppb for a patient with asthma and a FeNO below 40ppb	0.142	-	-	*Derived from the distribution around the mean FeNO level for patients with asthma*
Mean FeNO level for a non-asthmatic	25	Lognormal	μ = 2.77, σ = 0.94	*See section M.2.3.3 for derivation*
Probability that FeNO level < 25ppb for a patient without asthma and a FeNO level below 40ppb	0.823	-	-	*Derived from the distribution around the mean FeNO level for patients without asthma*
Strength of dependence between BDR and PEFv	0.1	Beta	α = 6.11, β = 54.96	GC opinion
Strength of dependence between PEFv and histamine/methacholine	0.5	Beta	α = 85.7, β = 85.7	GC opinion
Strength of dependence between BDR and	0.5	Beta	α = 85.7, β = 85.7	GC opinion

Parameter description	Point estimate	Probability distribution	Distribution parameters	Source
histamine/methacholine				
Proportion of non-asthmatic patients that have acute symptoms	0.25	Beta[(c)]	α = 78.16, β = 233.8	GC opinion
Proportion of non-asthmatic patients that have physical de-conditioning	0.25	Beta[(c)]	α = 78.16, β = 233.8	GC opinion
Proportion of non-asthmatic patients that have heart failure	0.25	Beta[(c)]	α = 78.16, β = 233.8	GC opinion
Proportion of non-asthmatic patients that have COPD	0.25	Beta[(c)]	α = 78.16, β = 233.8	GC opinion
Utility weights				
QoL increase from asthma treatment	0.0443	Beta	α = 23.86, β = 518.33	McTaggart et al[1113]
Disutility from severe exacerbation	0.56	Beta	α = 0.91 β = 71	Lloyd et al[1021]
Duration of severe exacerbation (in years)	0.08	Gamma	α = 19.26, λ = 246.34	Harnan 2014[637]
Disutility from non-severe exacerbation	0.32	Beta	α = 0.537, β = 1.14	Lloyd et al[1021]
Duration of non-severe exacerbation (years)	0.01	Gamma	α = 82.9, λ = 8259	Harnan 2014[637]
QoL increase for a mild severity COPD patient being correctly treated for COPD as opposed to asthma.	0.045	Beta	α = 23.83, β = 505.73	Spencer et al[1639]
QoL increase for a moderate severity COPD patient being correctly treated for COPD as opposed to asthma.	0.025	Beta	α = 24.35, β = 949.65	Spencer et al[1639]
QoL increase for a heart failure patient being correctly treated for heart failure as opposed to asthma.	0.098	Beta	α = 22.45, β = 206.65	Gohler et al[575]
Cost (£)[(b)]				
Cost of hospitalised exacerbation	£873.75	Gamma	α = 25, λ = 0.028	NHS reference costs[420] (weighted average of HRG codes DZ15H, DZ15J, DZ15K, DZ15L)
Cost of non-hospitalised exacerbation	£38.33	Gamma	α = 25, λ = 0.65	PSSRU[381], NHS drug tariff[1218]
Cost of spirometry	£16.86	Gamma	α = 100, λ = 5.93	GC opinion, PSSRU[381], NHS supply catalogue[422]
Cost of BDR	£26.16	Gamma	α = 100, λ = 3.82	GC opinion, PSSRU[381], NHS supply catalogue[422]
Cost of FeNO	£13.66	Gamma	α = 100, λ = 4.23	GC opinion, PSSRU[381], NHS supply catalogue[422]

Parameter description	Point estimate	Probability distribution	Distribution parameters	Source
Cost of PEF	£21.08	Gamma	α = 100, λ = 4.74	GC opinion, PSSRU[381], NHS supply catalogue[422]
Cost of Bronchial Challenge Studies, HRG code: DZ36Z	£102	Lognormal	α = 25, λ = 0.2451	NHS reference costs[421]
Cost of respiratory outpatient visit	£150.22	Gamma	α = 100, λ = 0.6657	NHS reference costs[420]
Cost of GP appointment	£37	-	-	PSSRU[381]
Cost of annual asthma management	£290.00	Gamma	See **Table 255**	Price et al[1386]
Cost of annual asthma management for patients without asthma but who have acute symptoms	£180.00	Gamma	See **Table 255**	Price et al[1386]
Cost of annual asthma management for patients without asthma but who have chronic symptoms	£248.91	Gamma	See **Table 255**	Price et al[1386]
Annual cost of COPD management for moderate severity	£307.74	Gamma	α = 25, λ = 0.08	NICE 2010 COPD guideline[1201]
Annual cost of COPD management for mild severity	£149.68	Gamma	α = 25, λ = 0.17	NICE 2010 COPD guideline (CG101)[1201]
Cost of heart failure treatment	£135	Gamma	α = 25, λ = 0.19	NICE 2014 Acute heart failure guideline (CG187)[1202]
Transition probabilities for Markov model and mortality adjustments				
Annual exacerbation rate for un-treated asthmatics	1.02	Lognormal	μ =0.02 , σ = 0.1	Harnan 2014[637]
Annual exacerbation rate for treated asthmatics	0.42	Lognormal	μ =-0.87 , σ = 0.2	Shaw et al[1558]
Probability of exacerbation for un-treated asthmatic per cycle	40%	-	-	*Derived from the exacerbation rate for un-treated asthmatics. See section (M.2.4)*
Probability of exacerbation for un-treated asthmatic per cycle	19%	-	-	*Derived from the exacerbation rate for un-treated asthmatics. See section (M.2.4)*
Proportion of exacerbations that are hospitalised	2.7%	Beta	R =40,243, n = 1474698	See section (M.2.3.6) for derivation and source input
Probability of death after hospitalisation	0.41%	Beta	R = 165, n =40,243	National review of asthma deaths 2014[1473]
Probability of correct re-diagnosis for patients with acute symptoms in 6 months	20%	Beta	α = 21.87, β = 87.47	GC opinion, see section M.2.3.5 for further details.
Probability of correct re-diagnosis for patients with	1%	Beta	α = 0.06, β =	GC opinion, see section M.2.3.5 for further

Parameter description	Point estimate	Probability distribution	Distribution parameters	Source
physical de-conditioning in 6 months			5.77	details.
Probability of correct re-diagnosis for patients with moderate COPD in 6 months	20%	Beta	α = 21.87, β = 87.47	GC opinion, see section M.2.3.5 for further details.
Probability of correct re-diagnosis for patients with mild COPD in 6 months	10%	Beta	α = 6.11, β = 55	GC opinion, see section M.2.3.5 for further details.
Probability of correct re-diagnosis for patients with heart failure in 6 months	30%	Beta	α = 21.87, β = 87.47	GC opinion, see section M.2.3.5 for further details.
Absolute probability increase of correct re-diagnosis after each 6-month cycle for patients with acute symptoms	20%	Beta	α = 21.87, β = 87.47	GC opinion, see section M.2.3.5 for further details.
Absolute probability increase of correct re-diagnosis after each 6-month cycle for patients with physical de-conditioning	0.5%	Beta	α = 0.01, β = 2.42	GC opinion, see section M.2.3.5 for further details.
Absolute probability increase of correct re-diagnosis after each 6-month cycle for patients with moderate COPD	20%	Beta	α = 21.87, β = 87.47	GC opinion, see section M.2.3.5 for further details.
Absolute probability increase of correct re-diagnosis after each 6-month cycle for patients with mild COPD	5%	Beta	α = 1.59, β = 30.17	GC opinion, see section M.2.3.5 for further details.
Absolute probability increase of correct re-diagnosis after each 6-month cycle for patients with heart failure	20%	Beta	α = 21.87, β = 87.47	GC opinion, see section M.2.3.5 for further details.
Hazard ratio of mortality for COPD patient	1.28	Lognormal	μ =0.247 , σ = 0.064	Diaz-Guzman et al[434]
Hazard ratio of mortality for patient with physical de-conditioning	1.18	Lognormal	μ =0.166 , σ = 0.028	Flegal 2013[498]
Hazard ratio of mortality for patient with chronic heart failure	2.1	Lognormal	μ =0.742 , σ = 0.103	Mosterd 2001[1171]

Abbreviations: BDR: bronchodilator reversibility; FeNO: fractional exhaled nitric oxide; PEF: peak expiratory flow variability

(a) This study found that the specificity of histamine and methacholine challenge tests were 100%. However the GC agreed that there is no perfect test so this value was reduced to 99% to reflect the high specificity but allowing some scope for error. This assumption was also incorporated into the beta distribution by changing the number of true negatives to achieve a specificity of 99%.

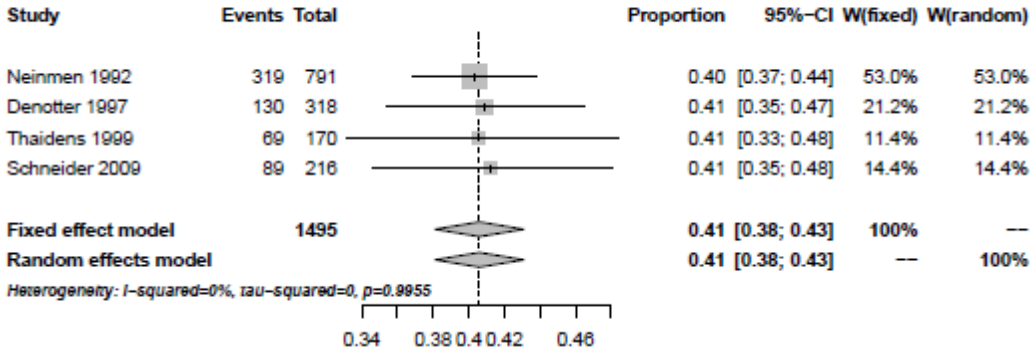
(b) These are costs of the tests as they appear in the pathway rather than the cost of conducting the test independently

(c) To ensure these values sum to one once a value has been chosen from each distribution the probability of having a particular disease becomes: $Prob(disease\ A) = Prob(disease\ A) / \sum Prob(disease_n)$ *where each probability is taken from its respective beta distribution.*

M.2.3.2 Initial cohort settings

The initial cohort settings were derived from information given in the studies included in our clinical review of diagnostic accuracy studies. The prevalence of asthma was obtained from a meta-analysis of all the included diagnostic studies which looked at the model's defined population. Ideally prevalence would be based only on UK studies, however no UK studies were included in the clinical reviews. To obtain a prevalence estimate applicable to the population in the model a few exclusion criteria were imposed. Firstly studies were excluded which only looked at children or looked at both adults and children and did not separate out the results. The prevalence of asthma is likely to deviate significantly between adults and children and therefore including child studies could bias the prevalence, most likely upwards. Secondly studies were included only if the inclusion criteria for patient entry into the study were patients presenting symptoms of asthma. For example if only patients with a normal spirometry were allowed to enter the study then the prevalence of asthma would fall as a significant portion of asthmatics have an obstructive spirometry. Finally as no study was conducted in the UK the GC agreed that studies which were conducted in Northern Europe, North America, Australia and New Zealand would give a better indication of asthma prevalence in the UK. Therefore studies outside of these areas were excluded when calculating asthma prevalence. The resulting meta-analysis is shown below in Figure 317 was based on four studies[417,1519,1728].

Figure 317: Meta-analysis for asthma prevalence



The majority of excluded studies had a lower prevalence rate ranging from 20% to 37%. Three studies had a prevalence of approximately 70% however they were all in Asian countries (Japan and S. Korea). It is worth noting a paper by Morice et al found asthma prevalence to be on average 25% across 13 studies in patients with chronic cough. This paper was not used in the base case as it is not clear what the exact recruitment methods were for patients into the studies, secondly patients entering the model are likely to exhibit other asthma symptoms rather than just a chronic cough. However this study suggests that the 41% estimate produced above is unlikely to be an underestimate of asthma prevalence in the defined population.

This value was also tested in the sensitivity analysis detailed in section M.2.5.

M.2.3.3 Diagnostic accuracies

Using diagnostic odds ratios to conduct probabilistic sensitivity analysis

The clinical review did not identify enough diagnostic studies to conduct meaningful diagnostic meta-analyses. Therefore, for each test included in the model the most relevant study used for the base case was identified as that which had: the correct cut-off, most relevant population and best reference standard. As there is no universally agreed reference standard for the diagnosis of asthma, the GC agreed that an appropriate reference standard would be an objective test alongside a physician diagnosis. The bronchodilator reversibility test was the only exception where an average was taken from the two studies identified in the clinical review. The reason was that the GC could not identify one study being more appropriate than the other, therefore an average was used in the base case and each separate set of diagnostic accuracies was used in a sensitivity analysis.

To account for uncertainty around diagnostic accuracies and correlation between sensitivity and specificity a joint distribution was used when making diagnostic accuracies probabilistic. The following method is outlined in Genders et al.[548] First of all the diagnostic odds ratio (DOR) was calculated for the diagnostic test:

$$DOR = \frac{sensitivity}{1 - sensitivity} * \frac{specificity}{1 - specificity}$$

The standard error of the log DOR was calculated using the absolute values for the number of TP, TN, FP and FN:

$$SE(\ln(DOR)) = \sqrt{\frac{1}{TP} + \frac{1}{FN} + \frac{1}{TN} + \frac{1}{FP}}$$

Using these equations a normal distribution was fitted using the log of the DOR and the standard error of ln(DOR). Once the DOR is calculated, the sensitivity can become a function of the DOR and the specificity:

$$sensitivity = 1 - \frac{specificity}{specificity + (1 - specificity) * DOR}$$

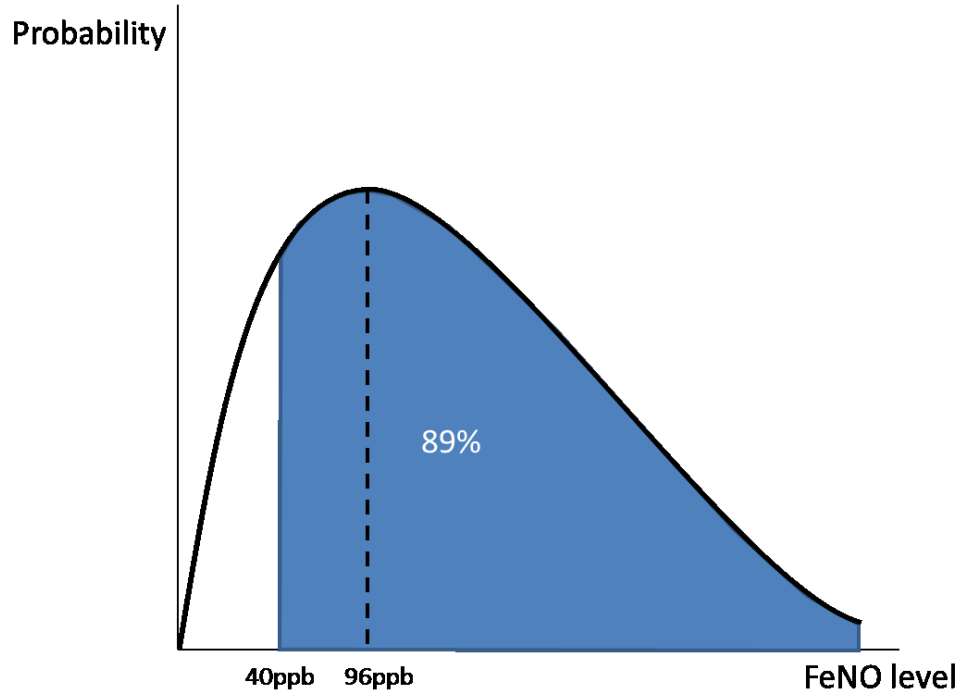
Finally a beta distribution was fitted around the specificity of the test, therefore when probabilistic sensitivity analysis is conducted the specificity will change in accordance to the overall diagnostic uncertainty and its relationship with the test sensitivity.

Using additional cut-offs for negative FeNO results

In some diagnostic strategies we had to take into account the probability of a FeNO level below 25ppb together with the probability of receiving a negative FeNO result (FeNO level < 40 ppb). The GC recognised that the lower an individual's FeNO level was the lower the probability the individual has asthma. Current guidelines[1536] recommend that an individual with a FeNO level below 25ppb is highly unlikely to have asthma. None of the studies identified in the clinical review gave a sensitivity and specificity at 25ppb cut-off. Therefore to calculate the probability of a patient with asthma producing a FeNO level below 25ppb two pieces of information were used:

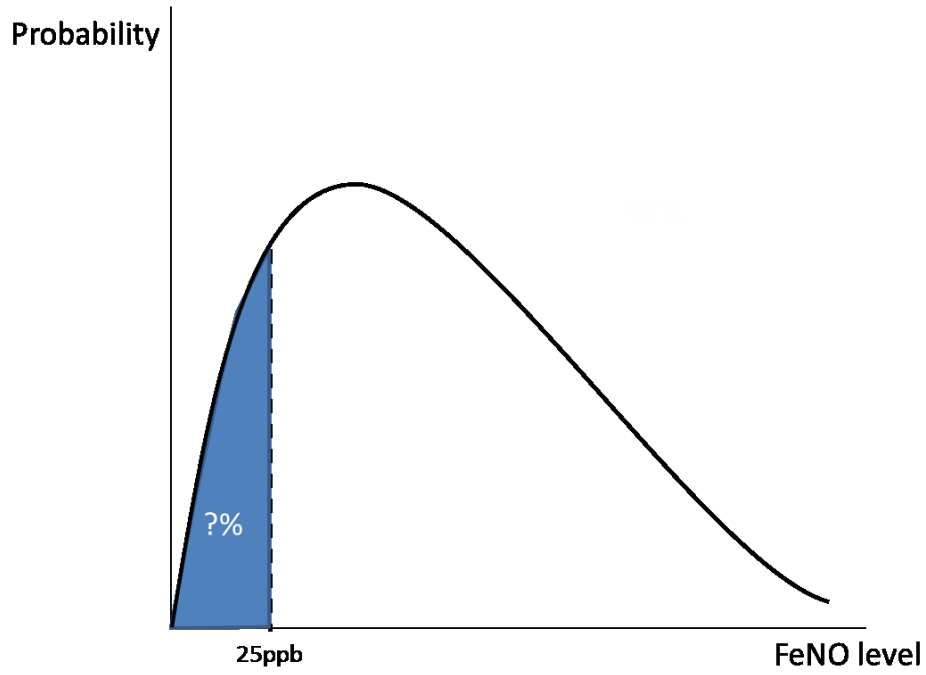
- The mean FeNO level for an asthmatic.
- The sensitivity of FeNO at a 40ppb cut-off.

Figure 318: Probability distribution of FeNO levels in individuals with asthma



As shown in Figure 318 above, using these two pieces of information a distribution was fitted around what FeNO level would be achieved by asthmatics. At 40ppb the sensitivity used for FeNO in the model was 89%. This means that the area under the curve highlighted in blue should equate to 89%. The mean FeNO level calculated for asthmatics in that study was 96ppb. As FeNO levels cannot go below zero a gamma and lognormal distribution were fitted to see which was more appropriate. A lognormal distribution was chosen as the gamma distribution gave a much higher probability to values close to zero whereas the lognormal gave a more even distribution amongst lower values. After this distribution was fitted, the final step was to calculate the proportion of patients with asthma that would produce a FeNO level below 25ppb.

Figure 319: Probability distribution of FeNO levels in individuals with asthma



As shown in Figure 319 above this was done by calculating the area under the distribution that fell to the left of 25ppb.

The same process was then completed for patients without asthma except this time the mean FeNO level for non-asthmatics and the specificity at a 40ppb cut-off (instead of the sensitivity) were used.

M.2.3.4 Mortality

For all patients at any point in the model the probability of death is determined by an age specific all-cause mortality rate. For patients with asthma the probability of death is also dependent on the probability of having a hospitalised exacerbation and the probability of death after hospitalisation. As exacerbation rates are higher in un-treated asthmatics, the overall probability of death calculated by the model is slightly higher for un-treated asthmatics compared to treated asthmatics. For non-asthmatics correct or incorrect treatment has no differential impact on mortality. Age-specific all-cause mortality, weighted for the gender split of the cohort population, was based on the most recent available life tables for England and Wales (2012-2013)[1260]. For non-asthmatic conditions hazard ratios were identified in the literature for patients with: COPD, chronic heart failure and de-conditioning. In the model the hazard ratio in people with obesity is used as a proxy for physical de-conditioning.

M.2.3.5 Re-diagnosis and exacerbation rates

The transition probability of re-diagnosis was determined through GC opinion. The transition probability for correct re-diagnosis for false negatives was calculated using an assumption whereby the probability of re-diagnosis is contingent on whether the patient has an exacerbation.

Exacerbation rates were taken from the clinical review conducted on monitoring asthma control. For individuals with asthma who remain untreated, due to a false negative diagnosis, the exacerbation rate was taken from Harnan et al.[637] As the exacerbation rate for untreated asthma was derived mostly from assumption, due to the lack of clinical data, this

value was extensively tested in a sensitivity analysis. A study by Shaw et al[1558] was chosen to reflect the exacerbation rates of a treated asthma patient as it was the most current study conducted in a UK setting. Once the exacerbation rates had been derived these were converted into transition probabilities for the respective cycle length (6 months) before inputting into the Markov model. The above conversion was done using the following formulae:

$Selected\ rate\ (r) = \frac{-\ln(1-P)}{t}$	Where *P*=probability of event over time *t* *t*=time over which probability occurs (1 year)
$Transition\ Probability\ (P) = 1 - e^{-rt}$	Where *r*=selected rate *t*=cycle length (6 months)

For false positives there was no clinical evidence to derive the length of time an individual would retain the incorrect asthma diagnosis for. The GC agreed this value would vary considerably, with some individuals being re-diagnosed within the year whereas others would retain the diagnosis for the rest of their life. The GC concurred that the probability of re-diagnosis would be contingent on the underlying condition causing the asthma symptoms to occur. As outlined in section M.2.2.1 four conditions were used in this model:

Heart failure

The GC considered that most individuals with heart failure would be re-diagnosed within a year and a few individuals may retain an asthma diagnosis beyond two years. To achieve this, an assumption was imposed that 30% of individuals would be re-diagnosed in the first 6 months and every 6 months the probability of re-diagnosis would increase by 20 percentage points. Therefore after two and a half years no individuals with heart failure would retain an asthma diagnosis in the model.

COPD

Individuals with mild COPD could remain misdiagnosed with asthma for a considerable length of time and the GC therefore gave a low probability of re-diagnosis every 6 months of 10%. Every 6 months the probability of re-diagnosis would increase by 5 percentage points as the GC considered that eventually a re-diagnosis would occur. Individuals with moderate COPD however would be re-diagnosed much sooner as their symptoms would appear far less well managed. Therefore the probability of re-diagnosis was set to 20% each 6 months and this increased by 10 percentage points for every 6 months after that.

Physical deconditioning

Individuals with physical deconditioning were the one group the GC agreed that re-diagnosis may never occur. Therefore the probability of re-diagnosis was set to a low 1% each 6 months and this only increased by 0.5 percentage points for every occurring 6 months.

Acute symptoms

Finally the GC agreed that individuals with acute symptoms would receive a re-diagnosis very quickly as symptoms would completely subside over a short period of time. Therefore the probability of re-diagnosis was set to 20% each 6 months and this increased by 20 percentage points for every occurring 6 months.

These values were extensively tested in a sensitivity analysis detailed in section M.2.5.

M.2.3.6 Utilities

Utility in people with asthma

The QoL for patients with asthma was derived from a systematic search of the literature. Only one study[1113] measured asthma utility in a UK population using EQ-5D with UK weights, as per the NICE reference case. The study details asthma utility for four levels of self-reported asthma control: uncontrolled, moderately controlled, well controlled and fully controlled as shown in **Table 242**.

Table 242: Quality of life and level of asthma control

Self-reported asthma control	Utility measured using EQ-5D
Very well controlled	0.9
Well controlled	0.84
Adequately controlled	0.81
Not controlled	0.8

Source: McTaggart et al (2008)[1113]

It was assumed that un-treated individuals with asthma will receive a QoL equal to a person with 'not controlled' asthma. Individuals that are treated for asthma will achieve a higher level of control. A study by Price et al details the proportion of patients being treated for asthma in the UK that are experiencing either: full control, partial control or uncontrolled asthma as shown in **Table 243:** .

Table 243: Levels of asthma control for treated patients with asthma

Asthma control	Proportion
Controlled	18.2%
Partially controlled	60%
Uncontrolled	21.8%

Source: Price et al[1386]

The study shows that while some patients achieve full control the majority achieve either partial control or remain uncontrolled. It was assumed that well controlled, detailed in **Table 242**, represents the QoL for partial control, and adequate control represents the QoL for uncontrolled, treated asthma. Therefore the health related quality of life (HRQoL) for treated asthmatics is:

$$HRQoL_{Treated} = Proportion(uncontrolled) * HRQoL(adequately\ controlled) + Proportion(partial\ control) * HRQoL(well\ controlled) + Proportion(controlled) * HRQoL(very\ well\ controlled)$$

Using the information detailed above the average HRQoL for treated asthma is 0.8443. Therefore the HRQoL increase for treating asthma is:

$$HRQoL_{Treated} - HRQoL(not\ controlled) = 0.8443 - 0.8 = 0.0443$$

Utility of exacerbation

One limitation with the EQ-5D questionnaire is that the individual is asked how their health is on that specific day when the questionnaire is administered. Therefore the EQ5D score

does not take into account the HRQoL impact from exacerbations (if the patient had no exacerbation on that day). A study by Lloyd et al[1021] derives an EQ-5D measure for exacerbations. Therefore in the model a patient receives a disutility if they experience an exacerbation. The size of this disutility is determined by whether the exacerbation is severe and therefore requiring hospitalisation and is weighted by the duration. The disutility is shown in **Table 244**.

Table 244: Disutility a patient experiences with an exacerbation

Severity of exacerbation	Quality of life decrease during exacerbation	Duration of exacerbation (years)	Disutility (QALYs)
Severe	0.56	0.08	0.0448
Non-severe	0.32	0.01	0.0032

Source: Lloyd et al[1021]

To calculate the proportion of adults that would have a hospitalised (severe) exacerbation, the proportion of hospitalised exacerbations was divided by the total number of exacerbations. The total number of exacerbations that occur each year was calculated by taking the annual probability of having an exacerbation and multiplying this by the number of adults with asthma in the UK (4.1 million taken from asthma UK). The annual probability of having an exacerbation was extracted from Shaw et al.[1558] The total number of annual hospitalisations in adults (40,243) was taken from the National review of Asthma deaths.[1473]

Utility of correctly treating non-asthmatics with asthma symptoms

For patients with COPD it is assumed that they will have either moderate or mild severity of COPD. In the model if the spirometry shows an obstruction an assumption was made that the patient would have moderate COPD whereas a spirometry showing no obstruction would indicate mild COPD. The quality of life associated with COPD severity is shown in Table 245.

Table 245: Quality of life for COPD patients by severity

COPD severity	Quality of life (SE)	Quality of life if treated for asthma
Mild	0.81 (0.02)	0.765
Moderate	0.72 (0.03)	0.695
Severe	0.67 (0.05)	NA

Source: Spencer et al[1639]

In the model if the patient has COPD but is treated for asthma then they will receive a QoL in between two severity levels, depending on how severe their COPD is. Therefore if a patient has mild COPD and is being treated for asthma they will receive a quality of life of 0.765, which is a quality of life half way between mild and moderate COPD. The GC decided to use the value half way between these points as asthma medication will slightly help treat COPD. Once the patient has been correctly re-diagnosed as having COPD their QoL will increase to the mean QoL for their severity level.

For patients with heart failure it was assumed that the majority would be classified under the New York Heart Association (NYHA) as class 2. Patients classified under NYHA class 1 are less likely to present any asthma related symptoms whereas patients with NYHA class 3 and 4 are likely to present non-asthma related symptoms that will indicate heart failure. The GC made an assumption that 80% of patients would be class II, 10% would be class I and 10% would be class III. The quality of life for each class is shown in Table 246.

Table 246: Quality of life by NYHA class

NYHA class	Quality of life (95% CI)	Quality of life if treated for asthma
I	0.855 (0.845 – 0.864)	0.771
II	0.771 (0.761 – 0.781)	0.673
III	0.673 (0.665 – 0.690)	0.532
IV	0.532 (0.480 – 0.584)	NA

Source: Gholer et al[575]

As the NYHA class the patient falls into is determined by the severity of their symptoms an assumption was used that patients who would fall under NYHA class II would have the quality of life of a patient with class III. Therefore a patient with class II heart failure being treated for asthma will have a QoL of 0.673. This QoL will increase to 0.770 once the patient has been correctly re-diagnosed and is treated accordingly.

These quality of life increases are extensively tested in the sensitivity analyses detailed in M.2.5.

Individuals with either acute symptoms or physical de-conditioning will receive no quality of life benefit from being correctly re-diagnosed as not having asthma. This is because any other management would not be mutually exclusive with asthma medication and therefore these costs and HRQoL benefits would occur in both true negatives and false positives leading to no incremental benefit. Individuals with 'acute symptoms' will therefore receive a quality of life equal to the general population 0.96. Individuals with physical deconditioning will receive a quality of life equal to the general population minus a disutility of 0.05. Both these values were taken from Harnan et al.[637] This disutility takes into account their symptoms and is thus equal to the disutility of having asthma. These values will not influence the cost-effectiveness of any strategy as they are not influenced by whether the individual is falsely diagnosed.

M.2.3.7 Resource use and costs

Diagnostic tests – primary care

For diagnostic tests conducted in primary care, resource use was elicited from the GC. This included information on: the health care professional who conducts the test, the time taken to administer the test, and the equipment used. Costs were then applied using data from the NHS supply chain catalogue[422] and the PSSRU[381]. Costs of individual tests conducted in primary care are reported below (Table 247 to Table 250). Training costs have not been included as a marginal cost, under the assumption that over time training costs marginalise to zero per patient.

Table 247: Cost of spirometry

Item	Quantity	Unit cost	Total Cost (quantity*unit cost)	Source
Time of GP practice nurse to conduct the test	20 minutes	£0.73 per minute	£14.66	GC opinion, PSSRU[381]
Micro-lab spirometer [(a)]	1/1500	£1498.90 per spirometer	£1.00	GC opinion, NHS supply catalogue[422]

Item	Quantity	Unit cost	Total Cost (quantity*unit cost)	Source
Bacterial filter, 3-litre syringe for calibration[(a)]	1/1500	£295.77 per syringe	£0.20	GC opinion, NHS supply catalogue[422]
Bacterial filter	1	£0.99 per filter	£0.99	NHS supply catalogue[422]
Total			**£16.86**	

(a) To calculate the marginal cost it was assumed that the equipment lasts for 5 years and is used on average 1500 times in this period.

Table 248: Cost of bronchodilator reversibility

Item	Quantity	Unit cost	Total Cost (quantity*unit cost)	Source
Time taken to administer bronchodilator and check for reversibility	20 minutes	£0.73 per minute	£14.66	GC opinion, PSSRU[381]
Volumatic spacer	1	£3.81 per spacer	£3.81	NHS supply catalogue[422]
MDI	1	£5.50 per MDI	£5.50	NHS supply catalogue[422]
Spirometry equipment to check for reversibility[(a)]	1	£2.19 (see **Table 247** above)	£2.19	NHS supply catalogue[422]
Total			**£26.16**	

(a) When a bronchodilator reversibility test is being performed in the model the first spirometry reading will have already been taken.

Table 249: Cost of FeNO

Item	Quantity	Unit cost	Total Cost (quantity*unit cost)	Source
Time taken to conduct test with GP practice nurse	10 minutes	£0.73 per minute	£7.30	GC opinion, PSSRU[381]
Marginal cost of using equipment (NIOX VERO[(a)])	1	£6.36 per use	£6.36	Harnan et al[637]
Total			**£13.66**	

(a) It was assumed that NIOX VERO is the most commonly used FeNO test

Table 250: Cost of peak expiratory flow variability

Item	Quantity	Unit cost	Total Cost (quantity*unit cost)	Source
Time taken to	10 minutes	£0.73 per minute	£7.30	GC opinion,

Item	Quantity	Unit cost	Total Cost (quantity*unit cost)	Source
instruct patient how to use test with GP practice nurse				PSSRU[381]
Time taken to interpret results by GP practice nurse	10 minutes	£0.73 per minute	£7.30	GC opinion, PSSRU[381]
Mini wright peak flow meter	1	£6.48 per meter	£6.48	NHS supply catalogue[422]
Total			**£21.08**	

Diagnostic tests – secondary care

The following tests are conducted in a secondary care setting. The costs of exercise and histamine/methacholine challenge tests are detailed in **Table 251** and **Table 252** respectively. It is assumed that a GP will refer a patient to have a challenge test and the patient will complete the test in a secondary care setting. The results of the test will be interpreted by a respiratory physician and sent back to the GP for analysis.

Table 251: Cost of exercise challenge test

Item	Quantity	Unit cost	Total cost	Source
Cost of interpreting result – 15 minutes of associate specialist time	1	£23.50	£23.50	GC opinion, PSSRU[381]
Investigation costs	1	£167	£167	NHS reference costs[420] - (Complex lung function exercise testing[(a)] HRG code: DZ31Z)
Cost of GP referral	1	£37	£37	GC opinion, PSSRU[381]
Total			**£227.50**	

(a) The HRG cost was weighted assuming that the test would only be conducted in outpatient and direct access

Table 252: Cost of histamine/methacholine

Item	Quantity	Unit cost	Total cost	Source
Cost of interpreting result – 15 minutes of associate specialist time	1	£23.50	£23.50	GC opinion, PSSRU[381]
Investigation costs	1	£102.00	£102.00	NHS reference costs[421]- (Bronchial challenge studies[(a)] HRG code: DZ36Z)
Cost of GP referral	1	£37	£37	GC opinion, PSSRU[381]
Total			**£162.50**	

(a) The HRG cost was chosen assuming that the test would only be conducted in directly accessed diagnostic services

To parameterise the reference costs probabilistically, the distribution of best fit was found by fitting a gamma and lognormal distribution. To fit each distribution, the standard deviation of the trust cost was estimated matching the reported interquartile ran ge to that calculated using the reported mean, and where appropriate the distribution's alpha and beta values. The distribution of best fit was that which provided the interquartile range of closest value to that reported by the NHS reference cost.

Cost of asthma treatment

The annual cost of asthma management was taken from a study by Price et al[1386]. A large driver of the cost of asthma management is the level of asthma control the individual achieves. Individuals achieving poor asthma control will have higher drug costs as they will be on a higher step of asthma medication receiving more expensive treatments. Likewise, individuals achieving good asthma control will have lower drug costs as they will be on a much less intensive form of treatment. The study by Price et al differentiates annual asthma costs by level of control and number of exacerbations. This annual cost incorporates: drug costs, GP consultations and hospitalisations and is shown in **Table 253**. N (%) represents the number and percentage of patients that fall in a particular cohort, mean (SD) represents the mean cost and its associated standard deviation.

Table 253: Annual asthma costs

		Number of exacerbations			
Level of GINA control		**0**	**1**	**2-3**	**4+**
Controlled	**N (%)** **Mean annual cost (SD)**	2583 (16.2%) £180 (£225)	196 (1.2%) £284 (£287)	38 (0.24%) £471 (£408)	13 (0.08%) £573 (£481)
Partially controlled	**N (%)** **Mean annual cost (SD)**	7079 (44.5%) £238 (279)	814 (5.1%) £397 (£358)	307 (1.9%) £557 (£427)	67 (0.42%) £645 (£549)
Uncontrolled	**N (%)** **Mean annual cost (SD)**	3642 (22.8%) £319 (£366)	745 (4.7%) £491 (£416)	399 (2.1%) £672 (£493)	102 (0.64%) £928 (£755)
Annual weighted asthma cost	£290				

Source: Price et al[1386]

Using this information the annual cost of asthma management can be calculated for the average asthma patient by taking a weighted average. This is done by weighting the cost of asthma management by the proportion of patients experiencing a certain number of exacerbations at a certain level of control. This average cost is equal to £290.

It was noted that since this cost was estimated the NICE asthma management guideline has recommended a cheaper treatment option that could effect approximately 30% of individuals with asthma. The recommendation suggest adding luketrine receptor agonists (LTRAs) instead of long-acting beta-agonists (LABAs) for those whose asthma remains uncontrolled on inhaled corticosteroids (ICS) alone. ICS+LTRA is approximatey 60% cheaper

than ICS+LABA. Therefore at most this recommendation will reduce the overall medication spend on asthma by 18% (60% cost reduction for 30% of people with asthma).

The impact to total asthma costs as measured above will be smaller as medication costs only represent a portion of the total asthma spend. The impact this development may have on the model results is explored in sensitivity analysis 8 by reducing overall asthma costs by 25%.

Annual cost of asthma treatment for non-asthmatics

Individuals who do not have asthma but are prescribed asthma medication (false positive) are likely to have a different annual cost compared to individuals with asthma. This has been incorporated into the model by extrapolating from the data presented in **Table 253**.

For individuals with acute symptoms they are likely to appear to be achieving full asthma control as their symptoms will pass with time. As they don't have asthma they will not experience any exacerbations. Therefore the cost given to these individuals in the model is the cost associated with controlled asthma and zero exacerbations which in **Table 253** is £180.

For individuals with either heart failure or physical de-conditioning their symptoms will be worse and it will appear that their asthma may be uncontrolled, however they won't experience any exacerbations. Therefore for these individuals a weighted cost of asthma management was calculated based on the number of individuals experiencing zero exacerbations but achieving differing levels of asthma control. As there is no data on the perceived level of asthma control achieved by non-asthmatics an assumption was made that the proportions achieving a certain level for control will be the same as asthmatics. This information is displayed in **Table 254** and has been extrapolated from the data presented in Table 253. The GC also noted that once the individual has been diagnosed with heart failure some individuals will retain their incorrect asthma diagnosis and remain on asthma treatment for the rest of their life. Therefore in the model 25% of the cost of asthma management will be retained after the individual has been diagnosed as having heart failure. This value was removed in a sensitivity analysis detailed in section M.2.5.

Table 254: Annual asthma costs for people with an incorrect diagnosis of asthma who have either heart failure or physical deconditioning

		Number of exacerbations
Level of GINA control		**0**
Controlled	(%) Mean (SD)	(19.4%) £180 (£225)
Partially controlled	(%) Mean (SD)	(53.2%) £238 (279)
Uncontrolled	(%) Mean (SD)	(27.4%) £319 (£366)
Annual average asthma cost	£248.91	

Finally for COPD patients it was assumed that if they were treated for asthma then they would incur the same costs as an asthma patient. This is likely to be an underestimate as COPD patients exacerbate more than asthma patients especially if they are being treated for

asthma as opposed to COPD. This will make the results more conservative for strategies with higher specificities.

These costs are tested in the sensitivity analysis in section M.2.5.

Adding uncertainty around asthma costs

As shown by the large standard deviations in **Table 253**, there is a great deal of uncertainty around the annual cost of asthma. This uncertainty was captured by attaching gamma distributions to each combination of control and exacerbation. The distribution parameters attached are shown in **Table 255**. Alpha and lambda parameters were calculated using the mean and standard deviation detailed in **Table 253**.

Table 255: Gamma distribution parameters for annual asthma costs[(a)]

Level of control/no. of exacerbations	Point estimate	Alpha	Lambda
Controlled / 0	£180	0.64	0.004
Partially controlled / 0	£238	0.72	0.003
Uncontrolled / 0	£319	0.76	0.002
Controlled / 1	£284	0.98	0.003
Partially controlled / 1	£397	1.23	0.003
Uncontrolled / 1	£491	1.39	0.003
Controlled / 2-3	£472	1.34	0.003
Partially controlled / 2-3	£557	1.7	0.003
Uncontrolled / 2-3	£672	1.86	0.003
Controlled / 4+	£573	1.4	0.002
Partially controlled / 4+	£645	1.38	0.002
Uncontrolled / 4+	£928	1.51	0.002

(a) Numbers are rounded to 2 decimal places or nearest integer

Annual cost of non-asthmatic treatment

For patients with COPD and heart failure once they are correctly re-diagnosed the NHS will incur the costs of their respective treatment rather than asthma medication.

The costs for COPD management were taken from the NICE COPD guideline.[1201] In the guideline the annual incremental costs of a patient with mild COPD, relative to the general population, were £149.68. For patients with moderate COPD this incremental cost increases to £307.74. Therefore in the model once a patient with COPD is correctly re-diagnosed and treated for COPD, the NHS will incur these costs rather than asthma management costs.

For heart failure patients the NHS will incur the cost of heart failure medication once the patient is correctly re-diagnosed. This cost was estimated to be £135 per year in the recent acute heart failure guideline[1202].

Cost of exacerbations

In the model exacerbation costs are calculated for patients who have an exacerbation whilst they are not being treated for asthma. This cost is dependent on whether the exacerbation is severe. If the exacerbation is not severe then the cost includes one GP appointment (£37 from PSSRU[381]) and a course of oral steroids with Prednisolone (cost=£1.33 from NHS drug

tariff[1218]). If the exacerbation is severe then the patient will be hospitalised and the cost of asthma hospitalisation will be added (cost = £873.74 from NHS reference cost[420]).

Therefore the average cost of an exacerbation is:

$$Average\ cost\ of\ exacerbation = Prob(hospitalisation) * cost(hospitalisation - \big(1 - Prob(Hospitalisation)\big) * cost(non - severe\ exacerbation)$$

Once the patient is being treated for asthma the exacerbation costs have already been taken into account as reported in Table 253 and therefore these costs as calculated above are excluded in these patients to avoid double counting.

M.2.4 Computations

The model was constructed in TreeAge Pro 2009[1765] and was evaluated by cohort simulation. Time dependency was built in by cross referencing the cohorts age as a respective risk factor for mortality.

QALYs for the cohort were computed each cycle. To calculate QALYs for each cycle, Q(t), the time spent in the alive state of the model was weighted by a utility value that is dependent on the time spent in the model and the health state. QALYs were then discounted to reflect time preference (discount rate = 3.5%) using the following formula:

$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$	Where: *r*=discount rate per annum *n*=time (years)

QALYs during the first cycle were not discounted. The total discounted QALYs were the sum of the discounted QALYs per cycle. The total discounted QALYs were the sum of the discounted QALYs per cycle.

Costs per cycle, C(t), were calculated in the same way as QALYs. Costs were discounted to reflect time preference (discount rate = 3.5%) in the same way as QALYs using the formula above.

Estimating cost-effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with two alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost-effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$ Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A	Cost-effective if: • ICER < Threshold

When there are more than two comparators, as in this analysis, options must be ranked in order of increasing cost then options ruled out by dominance or extended dominance before calculating ICERs excluding these options. An option is said to be dominated, and ruled out,

if another intervention is less costly and more effective. An option is said to be extendedly dominated if a combination of two other options would prove to be less costly and more effective.

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs (formula below). The decision rule then applied is that the comparator with the highest NMB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost.

$$Net\ Monetary\ Benefit\ (X) = (QALYs(X) \times \lambda) - Costs(X)$$

Where: λ = threshold (£20,000 per QALY gained)

Cost-effective if:
- Highest net benefit

Both methods of determining cost-effectiveness will identify exactly the same optimal strategy. For ease of computation NMB is used in this analysis to identify the optimal strategy.

Results are also presented graphically where total costs and total QALYs for each diagnostic strategy are shown. Comparisons not ruled out by dominance or extended dominance are joined by a line on the graph where the slope represents the incremental cost-effectiveness ratio.

M.2.5 Sensitivity analyses

The sensitivity analyses conducted below were undertaken to test some of the key assumptions employed in the model.

Table 256: Sensitivity analyses conducted

Analysis	Parameter	Description	Values	Comment
S1	Probability of COPD, physical deconditioning, heart failure or acute symptoms being cause of asthmatic symptoms	As the exact distribution of these underlying conditions is unknown this sensitivity analysis addresses different distributions between the four conditions. The model was run eight times with each condition being given a higher proportion (35%) once and a lower proportion (15%) once. The distribution between the remaining three conditions was set to be equal.	a) Probability of COPD being cause of symptoms: 15%, 35% b) Probability of obesity being cause of symptoms: 15%, 35% c) Probability of heart failure being cause of symptoms: 15%, 35% d) Probability of symptoms being	As there is no indication of what this distribution might be extreme values were run to cover a large range.

Analysis	Parameter	Description	Values	Comment
			acute: 15%, 35%	
S2	Sensitivity and specificity of bronchodilator reversibility	In the clinical review two papers were identified for bronchodilator reversibility that used the correct cut-off and had the right population. In the base case an average was taken of the two studies. This sensitivity analysis re-runs the model using both sources separately.	a) Sensitivity: 61% Specificity: 80% b) Sensitivity: 17% Specificity: 61%	Diagnostic accuracy taken from Chhabra et al[310] and Kim et al[861]
S3	Sensitivity and specificity of FeNO	In the clinical review one other paper was identified for FeNO that used the 40ppb cut-off and had the right population. The model was re-run using these values.	Sensitivity: 79% Specificity: 89%	Diagnostic accuracy taken from Fukuhara 2012[529]
S4	Sensitivity and specificity of MCT	In the clinical review one other study was identified for MCT that used the correct cut-off and had the right population. The model was re-run using these values.	Sensitivity: 97% Specificity: 83%	Diagnostic accuracy taken from Niemen 1992[1229]
S5	Sensitivity and specificity of spirometry	In the clinical review one other study was identified for spirometry that used the correct cut-off and had the right population. The model was re-run using these values.	Sensitivity: 29% Specificity: 59%	Diagnostic accuracy taken from Schneider 2009[1519]
S6	Probability of re-diagnosis for false positives.	This parameter was derived from clinical judgement as no data exists on what the real value is likely to be. Two scenarios were considered, one where re-diagnosis occurs much faster (probability of re-diagnosis is higher) and one where re-diagnosis occurs much slower (probability of re-	Probability of re-diagnosis is twice as likely, all relevant probabilities doubled. Probability of re-diagnosis is more unlikely, all relevant probabilities halved.	As there is no indication of what this value might be extreme values were run to cover a wide range.

Analysis	Parameter	Description	Values	Comment
		diagnosis is lower).		
S7	Probability of re-diagnosis for false negatives	This parameter was derived from clinical judgement as no data exists on what the real value is likely to be. An assumption was made that a patient with asthma would always be diagnosed within a year. This assumption was tested by running the model twice, once where this value is halved and once where this value is doubled.	Maximum length of time for an asthmatic to remain undiagnosed: 6 months, 2 years	As there is no indication of what this value might be extreme values were run to cover a wide range.
S8	Cost of asthma medication for false positives	This parameter was derived by extrapolating from robust data on annual asthma costs. Two scenarios were considered: one where asthma treatment costs were 25% higher and one where asthma treatment costs were 25% lower.	Asthma treatment costs for patients with COPD: £218, £363 Asthma treatment costs for patients with acute symptoms: £135, £225 Asthma treatment costs for patients with obesity: £186, £311 Asthma treatment costs for patients with heart failure: £186, £311	As there is no indication of what this value might be extreme values were run to cover a wide range.
S9	Strength of dependence between PEFv and BDR	This parameter was derived from clinical judgement as no data could be found on its exact value. This value was increased to reflect the possibility of PEFv results being more conditionally dependent on the result from BDR.	Strength of dependence between BDR and PEFv: 0.5	As there is no indication of what this value might be extreme values were run to cover a wide range.
S10	Strength of dependence between challenge tests and BDR	This parameter was derived from clinical judgement as no data could be found on its exact value. This value was increased to reflect	Strength of dependence between histamine challenge test and BDR: 0.75	As there is no indication of what this value might be extreme values were run to cover a wide range.

Analysis	Parameter	Description	Values	Comment
		the possibility of challenge test results being more conditionally dependent on the result from a BDR test.		
S11	Strength of dependence between challenge tests and PEFv	This parameter was derived from clinical judgement as no data could be found on its exact value. This value was increased to reflect the possibility of challenge test results being more conditionally dependent on the result from PEFv.	Strength of dependence between histamine challenge test and PEFv: 0.75	As there is no indication of what this value might be extreme values were run to cover a wide range.
S12	Quality of life improvement for COPD patients being correctly treated for COPD as opposed to asthma.	This parameter was extrapolated from the literature using GC opinion. Two sensitivities were run, one where QoL improvements for COPD patients are 50% higher and one were they are 50% lower.	QoL increase for a mild severity COPD patient being correctly treated: 0.01 – 0.06 QoL increase for a moderate COPD patient being correctly treated: 0.02 – 0.09	As there is no indication of what this value might be extreme values were run to cover a wide range.
S13	Quality of life improvement for heart failure patients being correctly treated for heart failure as opposed to asthma.	This parameter was extrapolated from the literature using GC opinion. Two sensitivities were run, one where QoL improvements for heart failure patients are 50% higher and one were they are 50% lower.	QoL increase for a heart failure patient being correctly treated: 0.04 – 0.15	As there is no indication of what this value might be extreme values were run to cover a wide range.
S14	Re-diagnosis costs	This parameter was extrapolated using GC opinion. Sensitivity was run where re-diagnosis costs only included one GP appointment. This can be seen as the minimum cost it could be.	Cost of re-diagnosis: £37	As there is no indication of what this value might be the lowest plausible estimate was used as an extreme value.
S15	Asthma prevalence	This parameter was derived from a meta-analysis. The model was re-run using the lower and upper limits of the 95% confidence	Asthma prevalence: 0.37, 0.43	

Analysis	Parameter	Description	Values	Comment
		interval.		
S16	Cost of methacholine challenge tests	A threshold analysis was run around the cost of methacholine challenge tests to see when treatment decisions would change.	Threshold analysis: Value run from £50 - £600	
S17	Conducting all primary care tests in one appointment	In the base case it was assumed that all primary care tests would be performed in one sitting. This sensitivity analysis adds the cost of one GP appointment to each primary care test	Cost of BDR, FeNO and PEFv increased by one GP appointment (£37)	
S18	Exacerbation rate for a untreated asthmatic	In the base case this value was based on weak data. For ethical reasons the exacerbation rate of an untreated asthmatic is unlikely to be known. The exacerbation rate for an untreated asthmatic will have an ambiguous effect on the model results as a high exacerbation rate is associated with disutility and a slightly higher mortality rate; however a high exacerbation rate means patients are re-diagnosed quicker which means a higher quality of life.	Threshold analysis: Exacerbation rate of untreated asthmatic run from 0.5 – 1.5.	As there is no indication of what this value might be extreme values were run to cover a wide range.
S19	Discount rate	Discount rate was changed from 3% for costs and QALYs to 1.5%. This is to reflect uncertainty around the true discount rate.	Discount rate: 1.5%	
S20	Probability that a heart failure patient retains an incorrect asthma diagnosis permenantly	The GC noted that even after the true cause of symptoms has been identified, some heart failure patients will incorrectly retain a diagnosis of asthma as the two diseases are not necessarily	Probability of heart failure patient retaining asthma diagnosis: 0%	

Analysis	Parameter	Description	Values	Comment
		mutually exclusive. In the base case this value was set as 25%. This assumption was removed in this sensitivity analysis.		
S21	Sensitivity and specificity of MCT	A two way sensitivity analysis was conducted on these two values running the diagnostic sensitivity from 90 – 98% and the specificity from 80 – 99%. This range covers the uncertainty surrounding what the diagnostic accuracy is of these tests in light of the clinical evidence and conditional dependence.	Sensitivity of MCT: 90-98% Specificity of MCT: 80-99%	
S22	Cost of FeNO	The cost of FeNO was based on the assumption that the test would be used 300 times per year. The marginal cost of FeNO was varied under the assumption that the number of uses per machine could be much lower.	Threshold analysis: Value run from £10 - £100	

M.2.6 Interpreting Results

NICE's report 'Social value judgements: principles for the development of NICE guidance'[1203] sets out the principles that GCs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost-effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

As we have several interventions, we use the NMB to rank the strategies on the basis of their relative cost-effectiveness. The highest NMB identifies the optimal strategy at a willingness to pay of £20,000 per QALY gained.

M.2.7 Model validation

The model was developed in consultation with the GC; model structure, inputs and results were presented to and discussed with the GC for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by a second experienced health economist from the NGC; this included systematic checking all of the model calculations.

M.3 Results

M.3.1 Base case

The results below in **Table 257** show that diagnostic strategy 3 has the highest net monetary benefit and is therefore the most cost-effective way of diagnosing asthma. Strategy 6 produces the highest number of QALYs however is not deemed cost-effective at a £20,000 per QALY threshold. Strategy 1 produces the least QALYs and the highest cost.

Table 257: Base case results (probabilistic)

Strategy	Mean per patient		NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
	QALYs	Cost			
Current practice	16.7766	£3,730	£331,802	6	6%
Strategy 1	16.7760	£3,753	£331,768	7	0%
Strategy 2	16.7776	£3,686	£331,866	5	19%
Strategy 3	16.7783	£3,683	£331,882	1	44%
Strategy 4	16.7785	£3,691	£331,878	4	0%
Strategy 5	16.7784	£3,686	£331,881	2	23%
Strategy 6	16.7787	£3,695	£331,879	3	8%

(a) Full details on each strategy is covered in section M.2.1.1

Figure 320 below shows the results from **Table 257** above on a cost-effectiveness plane. As you can see current practice and strategy 1 are dominated options, producing lower health gains at a higher cost relative to other strategies. Strategies 4 and 5 are extendedly dominated.

Figure 320: Cost-effectiveness plane showing incremental costs and QALYs of each individual strategy

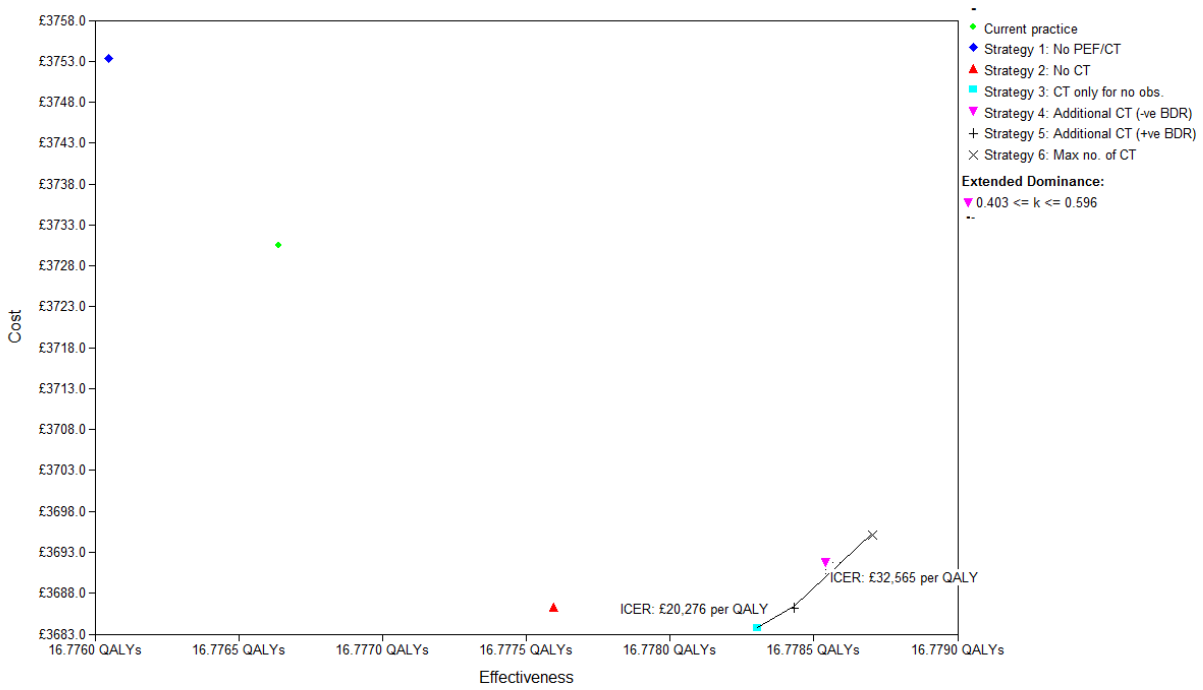


Table 258 below shows the overall sensitivity and specificity of each diagnostic pathway, that is the percentage of patients with asthma that receive a true positive diagnosis and the percentage of patients without asthma that receive a true negative diagnosis.

Table 258: Diagnostic accuracies of each strategy

	Current practice	Strategy 1	Strategy 2	Strategy 3	Strategy 4	Strategy 5	Strategy 6
Sensitivity	100%	90.3%	89.3%	86.3%	88.7%	87.7%	90.3%
Specificity	65.8%	69.1%	82.4%	89.5%	89.4%	89.4%	89.4%

Note: Accuracies rounded to one decimal place

Table 258 shows that no strategy has a single highest value for sensitivity and specificity though strategy 6 has the highest diagnostic odds ratio. Finally Table 259 details the cost of diagnostic tests associated with each strategy.

Table 259: Cost of testing in each strategy

	Current practice	Strategy 1	Strategy 2	Strategy 3	Strategy 4	Strategy 5	Strategy 6
Cost associated with diagnostic tests	£0	£42	£52	£92	£100	£95	£103

Table 259 shows that although the strategies that include challenge tests cost more the increase in cost is far less than the cost of a single challenge tests as the majority of individuals will not go on to receive one.

M.3.2 Sensitivity analyses

The following sensitivity analyses were run deterministically. Of the 22 sensitivity analyses conducted, as detailed in section M.2.5, the following resulted in a change in conclusions of the model . All other sensitivity analyses led to no change in the cost-effectiveness rankings of the strategies and therefore the model is robust to changes in those parameters.

S2a: Changing the sensitivity and specificity of BDR to 61% and 80% respectively.

Table 260 below shows the results of just the non-dominated strategies. As you can see strategy 5 is now the most cost-effective strategy at a £20,000 per QALY threshold. This is because a higher sensitivity of BDR means that more patients with asthma will receive a positive BDR result. As the pathway continues after a positive BDR it becomes more cost-effective to continue testing after negative test results to ensure false negatives are kept to a minimum. Likewise now the specificity is higher, more non-asthmatics receive a negative BDR result; therefore it becomes less cost-effective to continue testing after negative BDR results as the number of false negatives is already quite low.

Table 260: Results of sensitivity analysis S2a

Strategy	Mean per patient		ICER (per QALY gained)
	QALYs	Cost	
Strategy 3 (CT only after no obs)	16.8355	£3,550	-
Strategy 5 (additional CT after -ve BDR)	16.8357	£3,552	£10,667
Strategy 6 (largest amount of CT)	16.8358	£3,561	£56,755

S2b: Changing the sensitivity and specificity of BDR to 17% and 61% respectively.

Table 261 below shows the results of just the non-dominated strategies. Now strategy 5 is extendedly dominated . As the sensitivity of BDR is much lower very few asthmatics receive a positive BDR result. Likewise the low specificity means that lots of non-asthmatics will receive a positive BDR result. After a positive BDR test the individual will receive a FeNO test. If the FeNO comes out negative then, with these BDR diagnostic accuracies, it is highly likely that the individual does not have asthma thus making challenge testing beyond this point less cost-effective. Likewise as the majority of asthmatics will receive a negative BDR result it will be more cost-effective to keep testing beyond this point to ensure these false negatives are rectified.

Table 261: Results of sensitivity analysis S2b

Strategy	Mean per patient		ICER (per QALY gained)
	QALYs	Cost	
Strategy 3 (CT only after no obs)	16.7838	£3,692	-
Strategy 4 (additional CT after -ve BDR)	16.7841	£3,699	£24,281
Strategy 6 (largest amount of CT)	16.7842	£3,703	£60,422

S3: Changing the sensitivity and specificity of FeNO to 79% and 89% respectively.

The results in Table 262 show that the only non-dominated strategies are strategy 2, 5 and 6. As the FeNO specificity is much higher it becomes less cost-effective to continue testing after a positive result. Therefore if the individual has a non-obstructive spirometry and a positive FeNO then it becomes less cost-effective to continue testing after that point. Likewise a lower sensitivity means it is more cost-effective to keep testing after a negative FeNO result to ensure false negative results are reversed. Taking these two points into account strategy 3 becomes less cost-effective and strategies 5 and 6 become more cost-effective causing strategy 3 to become extendedly dominated.

Table 262: Results of sensitivity analysis S3

Strategy	Mean per patient		ICER (per QALY gained)
	QALYs	Cost	
Strategy 2 (No CT)	16.7832	£3,659	-
Strategy 5 (additional CT after +ve BDR)	16.7838	£3,670	£19,307
Strategy 6 (largest amount of CT)	16.7843	£3,684	£28,691

S4: Changing the sensitivity and specificity of MCT to 97% and 83% respectively

The results in Table 263 show that the results from the base case are sensitive to changes in the diagnostic accuracy of a methahcholine challenge test. In this sensitivity analysis the specificity is drastically decreased to 83%, from 99%. The sensitivity is increased however from 93% to 97%. As challenge tests are leading to fewer true negatives strategy 3 no longer dominates. It is worth noting that additional challenge tests after a bronchodilator reversibility test are no longer cost-effective. This is because although these additional challenge tests increase the sensitivity of the diagnostic pathway they now significantly reduce the specificity.

Table 263: Results of sensitivity analysis S4

Strategy	Mean per patient		ICER (per QALY gained)
	QALYs	Cost	
Strategy 2 (No CT)	16.7832	£3,692	-
Strategy 3 (CT only after no obs)	16.7838	£3,698	£8,530
Strategy 5 (additional CT after +ve BDR)	16.7840	£3,708	£62,477
Strategy 6 (largest amount of CT)	16.7840	£3,717	£170,957

S15: Threshold analysis on the cost of methacholine challenge test.

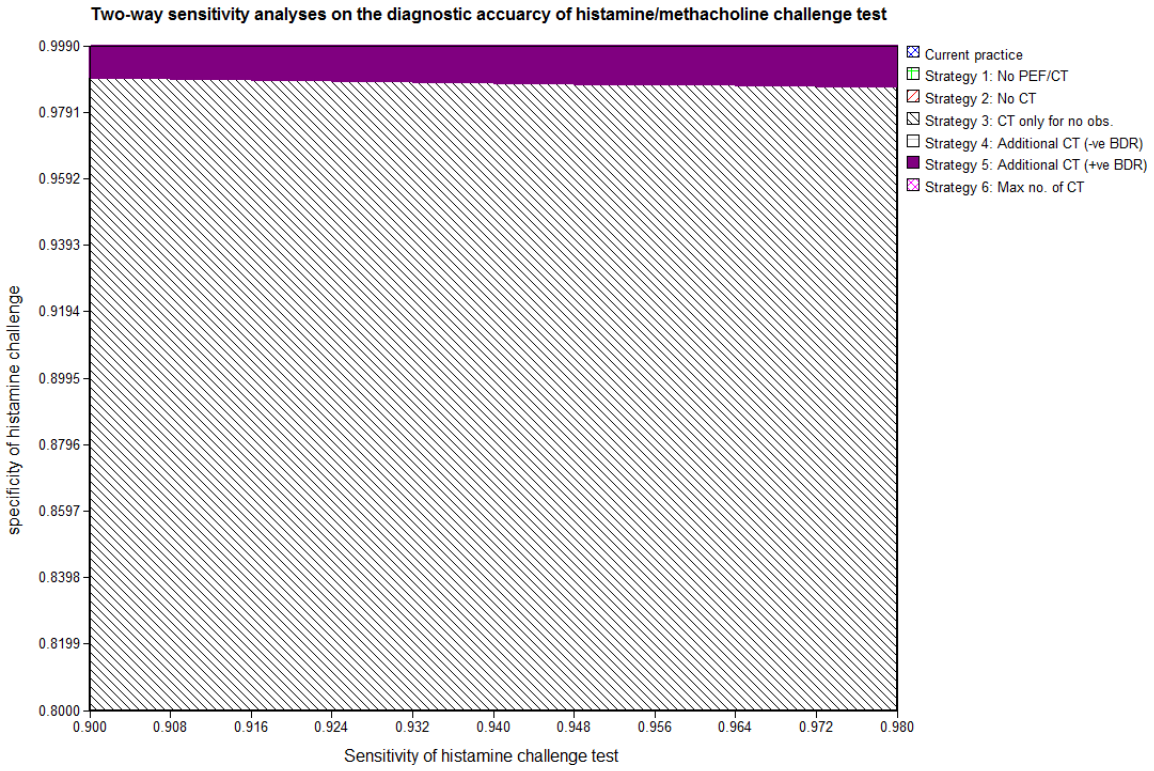
The sensitivity analysis showed that if the cost of a methacholine challenge test was £88 lower at £75 then strategy 6 (maximum number of challenge tests) becomes the new most cost-effective strategy. Likewise if the cost of the test was £87 higher at £240 then strategy 2 (no challenge tests) becomes the most cost-effective option. In reality as the methacholine challenge test is an infrequently used test; if this test was to be used more frequently then the costs could fall due to economies of scale. Therefore the likelihood of the test cost exceeding £240 is unlikely.

S20: Two way sensitivity analysis on the sensitivity and specificity of MCT

Figure 321 below shows the most cost-effective strategy for a range of different values used for the sensitivity and specificity of a MCT. The shaded colour indicates which strategy is

most cost-effective at particular co-ordinates on the graph, with sensitivity being on the x-axis and specificity being on the y-axis. The graph shows that challenge tests stil cost-effective if the sensitivity and specificity are far lower than the values used in the base case (93% sensitivity and 99% specificity). There is no clinical evidence to suggest the values are this low and conditional depdence would not cause the overall sensitivity AND specificity to decrease.

Figure 321: Two way sensitivity analysis on sensitivity and specificity of a MCT



S22: Changing the cost of FeNO

The marginal cost of FeNO was taken from the recent NICE DAP as detailed in Table 249. This marginal cost equated to £13.66 of which £6.36 was dedicated to the marginal cost per patient for the equipment use. When the cost of FeNO increased above £93 none of the diagnostic strategies were cost-effective at a £20,000 per QALY threshold and therefore current practice became the most cost-effective strategy. If the cost of FeNO was £93 then the cost-effective ranking of strategies remained unchanged. For the marginal cost of FeNO to rise to £93 the machine would only be used approximately 28 times in a 5 year time span. The GC noted that even for small GP practices under the most conservative assumptions of the number of new diagnoses made each year, this level of use would still be attainable.

M.4 Discussion

M.4.1 Summary of results

This analysis showed that providing challenge tests as part of a diagnostic pathway for individuals who present with asthma symptoms, have a non-obstructive spirometry and conflicting PEFv and FeNO results (strategy 3) is the most cost-effective strategy at a £20,000 per QALY threshold. Further challenge testing on patients with an obstructive spirometry provided higher health outcomes however was not cost-effective at a £20,000 per QALY threshold. All other strategies were either dominated or extendedly dominated.

The sensitivity analyses show that there is an element of uncertainty regarding the use of challenge tests for individuals who have an obstructive spirometry. The value of these additional challenge tests (those detailed in strategies 4, 5 and 6) is contingent on the diagnostic accuracy of bronchodilator reversibility tests, FeNO and methacholine challenge tests. This level of uncertainty has been captured in the recommendations whereby these tests are considered but not routinely offered.

In all sensitivity analysis a diagnostic pathway that incorparted challenge testing was always a cost-effective strategy. This is despite the fact there there are many aspects of the model that reduce the cost-effectiveness of challenge testing. For example it is assumed there is no mortality impact from falsely diagnosing individuals who have COPD and heart failure with asthma. Secondly the model does not cover all illnesses that could receive a false diagnosis of asthma. Conditions such as lung cancer and tuberculosis could have profound health consequences if misdiagnosed as asthma.

With regards to the routine use of challenge tests in asthma diagnosis for individuals with unobstructive spirometry (strategy 3) the model results are highly robust to changes in all key assumptions made within the model. Therefore although there is uncertainty regarding conditional dependence and the health and cost consequences of false diagnoses, solving this uncertainty will not change the conclusions of the model.

M.4.2 Limitations and interpretation

The main limitation with the model is the lack of clinical data available to inform some of the key parameters; mainly those surrounding misdiagnosis for non-asthmatics. To compensate for this, all the assumptions made have been conservative towards strategies that produce higher specificities. Firstly the model assumes that 50% of patients without asthma forego no quality of life from being diagnosed with asthma. In reality this number is likely to be an overestimate and there are likely to be some adverse effects of asthma medication as well that have not been captured. Secondly severe illnesses such as lung cancer have not been captured in this model which would have drastic quality of life impact if misdiagnosed as asthma. Finally no mortality effects have been captured for heart failure patients from foregoing correct treatment. All of this means that challenge testing for patients with non-obstructive spirometry is likely to be more cost-effective than is depicted in the model. It is worth noting that these limitations were extensively tested in the sensitivity analyses and challenge testing remained cost-effective at a £20,000 per QALY threshold in all of them.

Another limitation is that the evidence collected for the diagnostic accuracy of each test was not conducted in the appropriate subgroup of patients. For example in the diagnostic pathway ideally we would want to know the diagnostic accuracy of PEFv in a subgroup of patients who present symptoms of asthma and have no obstruction and a negative FeNO.

Instead the diagnostic accuracy was taken from a review on all patients who present asthma symptoms. This issue was tackled for the majority of tests, as detailed in section M.2.2.3, however conditional dependence was not fully incorporated for challenge tests in the model. A sensitivity analysis showed that both the sensitivity and specificity of a methacholine challenge test would have to decrease significantly to make them no longer cost-effective at a £20,000 per QALY threshold therefore indicating that conditional dependence is unlikely to have an impact of the model results.

M.4.3 Generalisability to other populations or settings

The results produced in this analysis are specific to a UK setting. To generalise the results to other countries the costs used and asthma prevalence parameter would need to be re-evaluated as these are likely to be country specific. Consideration also needs to be made as to how challenge tests are conducted. In this analysis it is assumed the GP refers the patient for the challenge test where it is performed and analysed in a secondary care setting. The results are then referred back to the GP where they discuss treatment options with the patient. Other methods of conducting the challenge test will have different cost implications and therefore make the results less generalizable to other settings.

It is worth noting that these results are not generalisable for children aged 16 or younger. The main reason for this is that the asthma prevalence in this population is very different. In a child population asthma is likely to be a much more common cause of a chronic cough. As asthma prevalence is higher this will increase the cost-effectiveness of more sensitive diagnostic strategies. Secondly children will not have other common conditions such COPD or heart failure for example. This will affect the final cost and health outcomes of each diagnostic strategy.

M.4.4 Comparisons with published studies

This is the first economic evaluation that addresses the cost-effectiveness of diagnostic pathways for diagnosing asthma. However other studies have attempted to assess the cost-effectiveness of asthma diagnostic tests on their own rather than as part of a pathway. To do this these studies have to make similar assumptions outlined in the methods above. Only one study attempts to do this and that is a study by Harnan et al.[637] The approach taken by Harnan et al was to assume that non-asthmatics had a disutility that remained until the correct diagnosis was made. This disutility was equal to the difference in quality of life between an asthmatic and a non-asthmatic. This approach attaches a much higher quality of life loss to incorrect diagnosis than the methods used in our model as it assumes all non-asthmatics will forego treatment that will cure them of their asthmatic symptoms. The approach by Harnan also overestimates the cost-savings to the NHS. If an individual is being treated for asthma then they forego correct medication, therefore the unnecessary asthma medication is a cost but there are savings being made by not prescribing the correct medication. The overall cost to the NHS from incorrectly prescribing asthma medication is therefore lower as money is not spent on the correct medication. Therefore relative to other methods the results produced in this analysis are much more conservative for strategies with higher specificities. As the results from Harnan et al are for singular diagnostic tests, their results are not comparable to the analysis presented above.

M.4.5 Conclusions

The main conclusion to be drawn from this model is that there is a place for routine challenge testing in a diagnostic pathway, despite its initial high cost. This is because its initial high costs are then offset by reduced unnecessary asthma management and a gain in QALYs. This conclusion was robust to a wide range of sensitivity analyses. A second important conclusion is that there is scope for further challenge tests, conducted on patients further down the pathway after an obstructive spirometry, to be cost-effective at a £20,000 per QALY threshold. In the base case the ICER for providing these extra challenge tests was £32,565 per QALY. However the sensitivity analyses showed there were some scenarios where it was cost-effective to do extra challenge tests, particularly for individuals who receive a positive bronchodilator result. The GC believed further challenge tests would be cost-effective in some situations. For example if another diagnosis, such as COPD, is considered likely then further challenge testing should not be considered. Therefore these additional challenge tests should not be routinely carried out, unlike those placed in strategy 3.

M.4.6 Implications for future research

Areas in the model that were most uncertain are difficult to resolve with further research due to ethical implications. For example the difference in quality of life between treated and untreated patients with asthma, or the quality of life lost by treating a heart failure patient with asthma medication. Although there was considerable uncertainty surrounding some diagnostic accuracies and conditional dependence the model results were robust to large changes in these parameters. Therefore additional research in these areas will not lead to any changes in management. One key area of uncertainty revolved around the diagnostic accuracy of mannitol. There was limited evidence on the diagnostic accuracy of mannitol and it is a cheaper test to perform relative to other challenge tests. There is also scope for mannitol to be conducted in primary care. If mannitol was proven to have a higher sensitivity and specificity then it could be a more cost-effective replacement for methacholine in the diagnostic pathway.

Appendix N: Research recommendations

N.1 High-priority research recommendations

N.1.1.1 **Research question 1:** What is the acceptability and diagnostic accuracy of objective tests that could be used to comprise a diagnostic pathway for asthma in children and young people aged 5 to 16 (for example, exercise challenge, direct bronchial challenge with histamine or methacholine, indirect bronchial challenge with mannitol and peripheral blood eosinophil count)?

Why this is important: Asthma is a common condition, diagnosed in nearly 1 in 10 children. There are no validated and reliable objective criteria for diagnosing asthma, so the vast majority of asthma diagnoses are currently based on symptoms and signs. However, symptoms and signs consistent with a diagnosis of asthma are not specific to the condition and can be present in other illnesses. This diagnostic uncertainty results in many children being incorrectly diagnosed with asthma, and many children with asthma in whom the diagnosis is delayed or missed. A single objective measure, or set of objective measures, that can be performed easily in non-specialist clinical settings (although it is noted that challenge tests need to be performed in specialist settings) will help improve diagnostic certainty and reduce the proportion of children treated inappropriately for asthma. This would ensure that children with the condition are identified and treated early.

Criteria for selecting high-priority research recommendations:

PICO question	**Population:** Children aged 5-16 years with respiratory symptoms. **Index test:** Exercise challenge, direct bronchial challenge with histamine or methacholine, indirect bronchial challenge with mannitol and peripheral blood eosinophil count. **Reference standard:** Physician diagnosis of asthma with an objective test (e.g. spirometry +/- BDR and FeNO test). **Outcome:** Diagnostic accuracy (sensitivity and specificity); serious adverse events; adverse events.
Importance to patients or the population	Correct and timely diagnosis of asthma in children will lead to appropriate treatment and improve patient outcomes.
Relevance to NICE guidance	Data from this research question will improve the sensitivity and specificity of the diagnostic algorithm in a future update of the NICE guideline.
Relevance to the NHS	Appropriate identification of children with asthma will reduce over-diagnosis and result in a reduction of inappropriate treatment. This will result in cost savings to the NHS.
National priorities	This is appropriate for the priority areas of improved management of long term conditions and reduction in respiratory morbidity and mortality.
Current evidence base	There is very little high quality data available on objective tests for the diagnosis of asthma in children aged 5-16 years. The current data available are inconsistent and are of limited utility in setting clear objective measurements in this age group.
Equality	n/a
Study design	This requires primary research in children who have clinical respiratory illnesses. Cross-sectional studies would be used for the assessment of the diagnostic accuracy of one (or a combination) of objective tests in the diagnosis of asthma or non-asthma, as determined by the reference standard. Randomised controlled trials could also be used to compare the downstream effects of test

	accuracy on patient outcomes.
Feasibility	Most secondary and tertiary clinical facilities will be able to participate in a multicentre study which would allow the rapid recruitment of the required number of children to give clear answers to the research question.
Other comments	Asthma is one of the most common clinical diagnoses made in children and leads to the prescription and consumption of preventive drugs that have known side-effects. Reduction in incorrect diagnosis of asthma could be viewed as a public health measure and the studies suggested would reduce the drug-load and cost-burden of unnecessary drugs.
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

N.1.1.2 **Research question 2:** What is the clinical and cost effectiveness of using an indirect bronchial challenge test with mannitol to diagnose asthma in adults (aged 17 and over)?

Why this is important: Chronic airway inflammation is associated with bronchial hyper-responsiveness, which is integral to defining asthma. Bronchial challenge testing can help diagnose asthma and assess response to inhaled corticosteroid therapy. It can also be used to monitor asthma control, alongside assessing symptoms and lung function. It is increasingly used in asthma management, although currently most tests are performed only in specialised centres or research settings.

Indirect challenge tests with inhaled mannitol act via active inflammatory cells and mediators, whereas direct challenge tests with inhaled histamine or methacholine act directly on bronchial smooth muscle. Indirect challenge testing is more specific but less sensitive than direct challenges.

Direct challenge testing may not identify a person who will respond to inhaled steroids. A positive result to an indirect challenge may reflect active airway inflammation that is likely to respond to inhaled corticosteroid therapy. Because a response to mannitol indicates active airway inflammation, identifying non-responsiveness in treated patients may help demonstrate good asthma control with inhaled corticosteroid therapy and identify people less likely to deteriorate after a dose reduction.

Mannitol bronchial challenge testing is quicker and simpler than current direct tests (which are generally confined to specialist respiratory centres), and uses a standardised inhaler device, so is potentially more useful in primary care.

Criteria for selecting high-priority research recommendations:

PICO question	**Population:** Adults and young people aged over 16 years with respiratory symptoms. **Index test:** Indirect BCT with mannitol. **Comparison:** Direct BCT with histamine or methacholine. **Reference standard:** Physician diagnosis of asthma with an objective test. **Outcome:** Diagnostic accuracy (sensitivity and specificity); adverse events.
Importance to patients or the population	Asthma is a treatable, but as yet incurable, chronic inflammatory condition of the lungs. A number of recent studies and reports highlight significant variations in the standard of care across the country with evidence that poor quality care is associated with worse outcomes, poorer quality of life and increased healthcare utilisation. Asthma is one of the most prevalent long-term conditions in the UK. It affects 5.4 million people, is a leading cause of avoidable hospital admissions, and is responsible for more than £1 billion of NHS spending every year. Premature

	mortality rates from asthma are over 1.5 times higher in the UK than in the rest of Europe, but there is no reason why the standard of care in the UK should be any lower than that of other European countries.[423,1911]
Relevance to NICE guidance	Clarification of the role of mannitol BCT both in terms of diagnostic accuracy compared to direct BCTs and as a potential tool in the monitoring of asthma would allow the NICE guideline on the diagnosis and monitoring of asthma to make firm recommendations regarding its use in clinical practice.
Relevance to the NHS	Asthma continues to result in a significant number of avoidable deaths, admissions and quality of life impairment, all with associated costs. Better diagnosis and monitoring of asthma will reduce healthcare utilisation, reduce the economic burden to the NHS and improve quality of life to people with asthma.
National priorities	The NHS Atlas of Variation in Healthcare demonstrates that there is significant variation in health outcomes for asthma across the NHS in England. The National Review of Asthma Deaths (NRAD)[1473] identified a number of quality and safety concerns related to the provision of asthma care in the UK. It raised particular concern around standards in primary care concluding that there was an urgent need to tackle 'complacency' about asthma.
Current evidence base	Indirect BCTs (such as mannitol) are more specific, though less sensitive, than direct BCT (such as methacholine, histamine) for identifying patients with active asthma. The potential for monitoring asthma with airway hyper-responsiveness is of particular interest to clinicians. Sont el al. demonstrated that management of asthma therapy based on reducing BHR in conjunction with symptoms and lung function leads to more effective control of asthma than management based on symptom control alone. The current evidence base suggests bronchial challenge testing is useful in the diagnosis of asthma. Mannitol BCT has high specificity for the diagnosis of asthma, although the sensitivity is only moderate when compared to direct BCTs (e.g. methacholine, histamine). The clinical efficacy and cost-effectiveness of mannitol BCT within a diagnostic algorithm for suspected asthma requires more research particularly in patients not receiving inhaled corticosteroids (ICS). The potential use of the mannitol challenge to assist monitoring of asthma in clinical practice is also of particular interest with respect to facilitating down titration of ICS and worthy of further research. The mannitol BCT provides a standardised, reproducible, rapid and simple test that does not require specialised equipment and may have some practical advantages, particularly for use in primary care.
Equality	Asthma affects all ages and ethnic groups, and the design of the research needs to encompass this.
Study design	Appropriately designed and powered real world randomised controlled trials: a) comparing mannitol BCT to direct BCT in the diagnosis of asthma in adults. b) comparing mannitol BCT to current recommended guideline based approach in the monitoring of asthma in adults. Particularly important outcome measures will include healthcare utilisation, exacerbation frequency, cumulative steroid burden (oral and inhaled) and cost-effectiveness.
Feasibility	Asthma is very common and uncontrolled in over half of all patients. Mannitol BCT was developed to solve some of the practical issues associated with other BCTs and to make BCTs more widely available to clinicians. It is feasible and practical to recommend future research in this area.
Other comments	None.
Importance	• High: the research is essential to inform future updates of key

	recommendations in the guideline.

N.1.1.3 **Research question 3:** What is the clinical and cost effectiveness of using electronic alert systems designed to monitor and improve adherence with regular inhaled maintenance therapy in people with asthma?

Why this is important: Adherence with regular maintenance inhaled corticosteroids, on their own or in combination with long-acting beta agonists, is of paramount importance to achieve control of asthma and prevent asthma attacks. Published evidence in patients with severe asthma suggests that at least 30% of patients are partially or non-adherent with their prescribed medications[1181], and the Royal College of Physicians' National Review of Asthma Deaths(NRAD)[1473] demonstrated that poor adherence was associated with 38% of asthma deaths.

Criteria for selecting high-priority research recommendations:

PICO question	**Population:** Adults, children and young people with mild to moderate asthma. **Intervention:** Monitoring adherence using different technologies/devices (eg prescription and refill monitoring systems; electronic monitoring inhalers). **Comparison:** Usual care; different frequencies of monitoring adherence using different technologies/devices. **Outcomes:** Mortality; QoL; exacerbations; unscheduled healthcare utilisation; adherence; asthma control.
Importance to patients or the population	Adherence with regular inhaled asthma therapies is suboptimal in a significant proportion of patients with asthma. Targetted intervention studies, that have improved adherence, have demonstrated a significant improvement in asthma control and reduced healthcare utilisation. Asthma outcomes have not improved in the last 15 years and the personal and economic costs of poor control are high. The efficient use of systems to monitor adherence and improve patient adherence and outcomes via feedback mechanisms, and the integration of these new technologies into healthcare are important for patients and for healthcare systems in terms of convenience, costs and outcomes.
Relevance to NICE guidance	Identification of clinically and cost-effective methods of monitoring adherence will allow the NICE guideline on Asthma: Diagnosis and Monitoring to make recommendations on the appropriate use of adherence monitoring strategies in NHS care.
Relevance to the NHS	Asthma continues to lead to avoidable deaths and considerable unscheduled health care utilization. Improved adherence with prescribed therapies will have a significant impact on health care utilization and improve asthma related quality of life.
National priorities	Reducing mortality considered amenable to healthcare is the overarching indicator of Domain 1 of the NHS Outcomes Framework, and poor adherence has been identified in the national review of Asthma deaths as a potentially avoidable factor in asthma deaths. Improving outcomes in asthma are highlighted in the National Strategy in COPD and Asthma as a national priority.
Current evidence base	There is a very limited current evidence base on the best monitoring method to monitor and feedback on a person's adherence to asthma maintenance therapy, in order to improve patient outcomes of QOL, morbidity and mortality. The majority of published studies have been conducted in patients with severe asthma, which comprise less than 5% of the asthma population. Further research is required to determine the optimal method of monitoring adherence for improving adherence and patient outcomes, particularly in people with mild to moderate asthma.

Equality	Asthma affects all ages and ethnic groups, and the design of the research needs to encompass this. In particular, the study of adherence monitoring interventions needs to ensure that the programmes are accessible to those with learning and physical disabilities, non-English speakers, different age groups and those with health literacy problems.
Study design	Cluster randomised controlled trials comparing monitoring adherence using different technologies/devices. Implicit in the investigation of the best monitoring method or device, is that poor adherers will be detected and feedback will improve adherence to controller medication and therefore improve patient outcomes and asthma control. A range of studies may be needed, including 'efficacy' trials and more pragmatic 'real-world' effectiveness and implementation trials. Studies will need to compare the different devices/strategies that are currently available to monitor adherence and feedback this information to patients with the aim of improving adherence and patient outcomes. Studies need to include health economic evaluation and be of sufficient duration to confirm persistence of benefit (minimum of 12 months). Studies should be adequately powered to detect sub-groups who are likely to respond or not respond to this strategy.
Feasibility	Asthma is common and uncontrolled in over half of all patients. Multiple different technologies to monitor adherence are already available.
Other comments	There are commercial implications to technologies designed to monitor adherence and commercial partnership is possible. Intellectual property rights issues will need to be considered.
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

N.1.1.4 **Research question 4:** What is the current frequency and the current method being used to check the inhaler technique of people with asthma? What is the optimal frequency and the best method of checking inhaler technique to improve clinical outcomes for people with asthma?

Why this is important: Knowing and understanding how to use an inhaler properly is the cornerstone of asthma management and symptom control. There has been an increase in the types of inhaler devices and the types of delivery system available. The various types of drugs for asthma control are also available in different inhaler devices on their own and in a combination of 2 drugs. It is therefore vital for patients to learn the proper inhaler technique for their device to ensure optimum drug delivery to the lungs for asthma control.

Criteria for selecting high-priority research recommendations:

PICO question	**Population:** Adults, children and young people aged 5-16 years with a confirmed diagnosis of asthma; children 0-5 years with recurrent wheeze. **Intervention:** Electronic devices to monitor inhaler technique; visual assessment by doctor, nurse or pharmacist. **Comparison:** Different frequencies of monitoring inhaler technique; monitoring using electronic devices vs. monitoring by visual assessment. **Outcomes:** Mortality; QoL; exacerbations; unscheduled healthcare utilisation; adherence; asthma control.
Importance to patients or the population	Proper inhaler technique for optimum drug delivery to the lungs of people with asthma is vital for asthma control. Asthma exacerbations can occur frequently if not properly controlled. This has a significant impact on the quality of life and constitutes a considerable healthcare burden with pressures on secondary care emergency departments. There is a lack of objective evidence that regular review of inhaler technique improves asthma control and reduces exacerbations.

	This is important because checking inhaler technique is a simple intervention that if effective could result in lower doses of inhaled steroids to control the asthma and in a reduction of acute exacerbations.
Relevance to NICE guidance	The answer to this question will allow NICE to make a definitive statement on the optimal frequency and the best method of checking inhaler technique to improve clinical outcome for people with asthma.
Relevance to the NHS	Acute asthma attacks are one of the commonest reasons for visits to hospital emergency departments. The most expensive expenditure for the NHS is on prescribing the inhaled drugs used for respiratory conditions. It is estimated that the top three most expensive drugs in the NHS are inhalers. It is important to teach patients with asthma the correct technique for using their inhalers. It is equally important to review their inhaler technique regularly. Current guidance is to check the patient's inhaler technique annually. The inhalers should only be prescribed after patient has received training in the use of the device and have demonstrated satisfactory technique. Satisfactory understanding of individual inhaler techniques and regular checking by the clinicians and pharmacists is vital to improving clinical outcomes for control of asthma.
National priorities	The intervention is simple and could result in better asthma control without increasing medication use. The 'prescribing and medicine uses' recommendation from NRAD (National Review of Asthma Deaths)[1473] is to assess inhaler technique routinely and formally document at every annual review. It should also be checked by the pharmacist when a new device is dispensed.
Current evidence base	There is a lack of good quality data available. Different studies used non-standardised scores making comparisons difficult. Teaching inhaler technique has been shown to improve correct usage but it is less clear if that leads to improved asthma control. For 'monitoring inhaler technique vs no monitoring' evidence was only available in adults from one small RCT and evidence was of low and very low quality for all outcomes. For 'Monitoring using an electronic training device and physician feedback compared to physician feedback only', evidence in adults was available from 2 studies, and in children from 1 study. Evidence for all outcomes was of low and very low quality. Based on the NRAD report, people with asthma who are unable to use their inhaler correctly are at risk of poor asthma control, potentially resulting in an asthma attack. It is recorded in the report that only 96 out of 135 (71%) patients had an assessment of inhaler technique.
Equality	Asthma affects all ages and ethnic groups, and the design of the research needs to encompass this. In particular, the study needs to ensure that the programmes are accessible to those with learning and physical disabilities, non-English speakers, different age groups and those with health literacy problems.
Study design	A systematic review is needed first to elucidate the current frequency and the current method being used to check inhaler technique. This will inform randomised control trials to investigate the optimal frequency and best method of checking inhaler technique.
Feasibility	Due to the multiple different types of inhaler currently available it will be difficult to develop a single study to answer this critical research question. However, it will be possible to look at dry powder and metered dose inhalers separately to address the issues of how best to teach inhaler technique and the optimal frequency for monitoring it. All primary and secondary care facilities will be able to participate in a multicentre study which would allow the rapid recruitment of the required number of participants to give a clear answer to the research question.

Other comments	It is important to study simple techniques that improve control without increases in steroid medication. Trials to check inhaler technique for monitoring asthma control will attract commercial sponsors. However given the size of the problem, the potential impact to the patients and the NHS and the favourable policy context, a high quality study addressing this question would be an appropriate target for NIHR funding.
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

N.1.1.5 **Research question 5:** What is the long-term (more than 12 months) clinical and cost effectiveness of using tele-healthcare as a means to monitor asthma control in adults, young people and children? Methods of tele-healthcare can include telephone interview (with healthcare professional involvement) and internet or smartphone-based monitoring support (no healthcare professional involvement).

Why this is important: Asthma outcomes have not improved in the past 15 years, and the personal and economic costs of poor control are high. Computers and smartphones play an ever-greater role in modern life, with a growing proportion of people using them regularly for work, leisure, communication and information. The efficient use of distance monitoring systems and the integration of new technologies into healthcare are important for patients and for healthcare systems in terms of convenience, costs and outcomes.

Criteria for selecting high-priority research recommendations:

PICO question	**Population:** Adults, children and young people with a confirmed diagnosis of asthma. **Intervention:** Monitoring asthma control using telephone interview with a healthcare professional and internet/smartphone-based monitoring support. **Comparison:** Usual care; monitoring asthma control with healthcare professional involvement e.g. telephone interview vs. monitoring asthma control with no healthcare professional involvement e.g. internet/smartphone-based monitoring support. **Outcome:** Mortality; QoL; exacerbations; unscheduled healthcare utilisation; adherence; asthma control.
Importance to patients or the population	Asthma is a long-term and incurable condition, and outcomes remain sub-optimal. Regular monitoring and self-management are recommended in guidelines to improve outcomes, but can be difficult to achieve in practice. New technologies can be used to improve communication between patient and clinician and to provide individualised education and self-management support.
Relevance to NICE guidance	Clarification of the role of tele-healthcare in asthma will allow the NICE guidelines relating to the diagnosis and monitoring of asthma to make recommendations on the appropriate use of tele-healthcare strategies in NHS care.
Relevance to the NHS	Asthma continues to result in avoidable deaths, admissions and quality of life impairment, all with associated costs. More efficient monitoring can allow proactive care to prevent adverse outcomes and so potentially reduces health resource use and costs by more efficient care.
National priorities	Reducing mortality considered amenable to healthcare is the overarching indicator of Domain 1 of the NHS Outcomes Framework, and inadequate monitoring has been identified in the national review of Asthma deaths as a potentially avoidable factor in asthma deaths. Improving outcomes in asthma are highlighted in the National Strategy in COPD and Asthma as a national priority.

Current evidence base	The current evidence base of tele-healthcare in asthma is inadequate and contradictory; some studies have indicated potential benefits, but some have not. Further research is required to identify the modality of tele-healthcare that is most effective (e.g. telephone support, internet/smartphone based monitoring and self-management support), qualifying the acceptability, benefits, risks and costs associated with different programmes in different patient groups.
Equality	Asthma affects all ages and ethnic groups, and the design of the research needs to encompass this. In particular, the study of digital technology interventions needs to ensure that the programmes are accessible to those with learning and physical disabilities, non-English speakers, different age groups and those with health literacy problems.
Study design	Appropriately designed and powered randomised controlled trials comparing tele-healthcare interventions with usual care and with other monitoring strategies. A range of studies may be needed, including 'efficacy' trials and more pragmatic 'real-world' effectiveness and implementation trials. Cluster randomisation is likely to be needed to prevent 'contamination' of control groups. Studies need to include health economic evaluation and be of sufficient length to confirm persistence of benefit (minimum of 12 months). Studies should be adequately powered to detect sub-groups who are likely to respond or not respond to this strategy.
Feasibility	Asthma is very common and uncontrolled in over half of all patients. With technological advances, access to tele-healthcare and digital technologies is common and relatively inexpensive.
Other comments	There are potential commercial implications to tele-healthcare monitoring systems, and commercial partnership is possible. IPR issues will need to be carefully considered.
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

N.2 Other research recommendations

6. What is the clinical and cost effectiveness of using validated quality of life questionnaires and the RCP 3 Questions as tools to monitor asthma control in adults and young people aged over 16 years?
7. What is the clinical and cost effectiveness of using validated paediatric questionnaires to monitor asthma control in children aged 5-16 years old with asthma?
8. What is the clinical and cost effectiveness of using blood eosinophils as a tool to monitor asthma control?
9. Which patient groups are likely to benefit from FeNO monitoring to guide asthma management, for example, individuals with atopy, frequent asthma attacks, poor adherence?
10. What is the clinical and cost effectiveness of FeNO-guided monitoring of asthma in real-world settings?

Appendix O: Contributors to the guideline

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Stakeholders

- Aerocrine
- Alder Hey Children's Hospital, Liverpool
- Association for Respiratory Technology & Physiology (incorporating the views of the Global Lung Initiative Group)
- Association of Respiratory Nurse Specialists
- Asthma UK
- Astrazeneca
- Boehringer Ingelheim Ltd
- British Medical Association
- British Paediatric Respiratory Society
- British Society for Allergy & Clinical Immunology
- British Thoracic Society
- Cochrane Airways Group
- Department of Health
- Department of Health, Social Services and Public Safety - Northern Ireland
- DGH
- Digital Assessment Service, NHS Choices
- Durham Dales, Easington and Sedgefield
- Education for Health
- Faculty of Pharmaceutical Medicine
- Faculty of Sport and Exercise Medicine
- Group of Occupational Respiratory Disease Specialists
- HQT Diagnostics
- Leeds Teaching Hospitals NHS Trust
- London Respiratory Network
- Manchester University
- Mid Yorkshire NHS Trust
- Napp Pharmaceuticals
- National Inhaler Group

- National Paediatric Respiratory and Allergy Nurses Group (NPRANG)
- Neonatal and Paediatric Pharmacists Group (NPPG)
- News reporter for GP Magazine David Millett
- NHS England
- NHS Stockport CCG
- NORTH EAST LONDON FOUNDATION TRUST
- North West Severe Asthma Network
- Novartis Pharmaceuticals UK Ltd
- Orion Pharma UK Ltd
- Oxford Centre for Respiratory Medicine
- Primary Care Respiratory Society UK
- RCP NRAD 2014 Clinical Lead
- Royal College of General Practitioners
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- Royal College of Paediatrics and Child Health
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- Royal College of Physicians
- Scottish Intercollegiate Guidelines Network (SIGN)
- South eastern Hampshire CCG
- The Anaphylaxis Campaign
- The National Allergy Strategy Group
- Thermo Fisher Scientific
- UHL
- United Kingdom Clinical Pharmacy Association Respiratory Group

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Appendix Q: Feasibility report

NICE National Institute for Health and Care Excellence

Asthma: diagnosis and monitoring guideline
Primary care implementation feasibility project

January 2017

Asthma: diagnosis and monitoring guideline

Primary care implementation feasibility project

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1. Background and aims

In January 2015, NICE issued a draft guideline on asthma diagnosis and monitoring. During consultation, stakeholders suggested a large investment in training and equipment would be needed to bring current practice in line with the guideline's diagnostic test recommendations, and that this was likely to be a major burden for primary care services and a barrier to implementation.

In August 2015 the guideline was paused to allow additional time to work with primary care professionals to assess the feasibility of adopting the diagnostic recommendations. These recommendations included use of 2 objective tests; spirometry and fractional exhaled nitric oxide (FeNO).

The interim findings guideline was published in January 2016. This made some revisions to the diagnostic algorithms, with advice to treat acutely unwell people on presentation immediately without waiting for objective tests, but to not make a formal diagnosis of asthma until objective tests have been done.

The Adoption and Impact team at NICE ran a feasibility project to test the diagnostic algorithms published in the interim findings guideline:

- Assess the impact and feasibility of adopting the technical diagnostic tests (spirometry and FeNO) recommended in the proposed asthma diagnostic guideline into primary care.
- Report the field testing findings back to NICE's Centre for Guidelines and the Guideline Development Group by the end of 2016. The findings would be used to help guide their review of the guideline recommendations in time for publication alongside the asthma management guideline in July 2017.
- Demonstrate that NICE has proactively responded to their comments.

An asthma feasibility project team was formed within the NICE Adoption and Impact team. The project team designed the feasibility project and worked with 7 primary care sites across England, who agreed to implement the revised diagnostic recommendations (including the 2 objective tests) and algorithms. Outcome data was collected for the 6-month period May to October 2016. This report is the findings from this work.

2. Methods

Site recruitment

On 25 January 2016, NICE advertised for GP practices in England interested in taking part in the primary care implementation feasibility project. This was done using the following communication channels:

- a dedicated project webpage on the NICE website
- the NICE Update for Primary Care newsletter
- the NICE GP newsletter
- the NICE Twitter feed
- NICE implementation field team contacts in local clinical commissioning groups (CCGs)
- a Primary Care Respiratory Society and Asthma UK member update.

In all, 78 expressions of interest were received before the closing date (27 February 2016). Of these, 69 were from individual GP practices and 9 were from sites which covered 2 or more practices. The practices and sites were spread across England: Yorkshire and Humber (6), West Midlands (9), South West (24), East Midlands (5), East of England (4), London (3), North East (4), North West (17), South East (6).

Site selection

Shortlisting criteria was focused around demographic characteristics to ensure feasibility was tested in a variety of settings. Consideration was given to:

- the size of the site or practice (patient numbers)
- geographical location (across England)
- the percentage of patients with an existing asthma diagnosis
- the practice's current care pathway for diagnosis of asthma
- registered patient characteristics (deprivation scores, ethnicity and age)
- the application form being fully completed and no conflicts of interest given
- the site or practice being able to provide retrospective baseline data.

Applications were automatically rejected if there were any relevant conflicts of interest in relation to this project (for example, any commercial interests with FeNO

testing), if retrospective baseline data was not available or if application forms were incomplete.

Shortlisted sites had a phone interview with 2 members of the asthma feasibility project team. The eventual cohort was selected on the basis of practice characteristics, rather than the perceived quality of their asthma service (see table 1).

Selected sites

A total of 7 sites across England were selected (see figure 1). Some sites consisted of more than 1 individual practice. Their identity was kept confidential both internally and externally during the project to allow the sites to implement the recommendations without any external influences.

Figure 1: Geographical location of each site

Site preparation

Sites were asked to implement the diagnostic recommendations and algorithms from the interim findings guideline, with a specific focus on the spirometry and FeNO recommendations.

Sites were advised that NICE would not influence or dictate how they should implement these recommendations in terms of service model or staffing, and that the purpose of the project was to evaluate the feasibility of implementation only.

All sites were visited by 2 members of the asthma feasibility project team before the project started, and were given a full information pack including instructions for data collection. During this visit current service provision and levels of training were discussed and recorded.

Financial support

Financial support of £3,000 per project site was made available to help with local data collection, payable upon completion of the project.

Diagnostic tests

Spirometry

Spirometry is a physiological test that measures how much air a person can breathe in and out (volume), and how quickly they can do this (flow). The primary measurement in spirometry may be volume or flow. All sites had their own spirometry equipment.

The draft NICE guideline does not specify any minimum requirements for spirometry training[a] and so no minimum training standard was imposed for this project.

Because access to quality-assured diagnostic spirometry was an issue highlighted during consultation, NICE offered to reimburse funding for accredited Association for Respiratory Technology and Physiology (ARTP)/British Thoracic Society (BTS) spirometry training and registration for certification for key staff at the project sites. This funding was given if the training element was completed by the end of the delivery part of the project, and was in addition to the financial payment made. Sites were given the contact details of their nearest ARTP training centres and online training options, and were asked to organise this themselves.

[a] The full guideline states that tests of pulmonary function should be carried out by appropriately trained staff with appropriate equipment, who are able to assess the correct performance of the test by the patient and the quality of the results.

Sites were under no obligation to take this training regardless of their current level of competence. This was because variation in competency reflects real-world variation.

In September 2016 'Improving the quality of diagnostic spirometry in adults: the National Register of certified professionals and operators' was published. This competency assessment framework for diagnostic spirometry was co-produced by a stakeholder group and endorsed by NHS England. This states that diagnostic spirometry should be quality assured and only performed and interpreted by professionals assessed as competent against recognised standards. The framework sets out the new arrangements for diagnostic spirometry, which will be phased in from April 2017 to March 2021. Key to this framework is the establishment of a national register of certified healthcare professionals and operators. This register will ensure that commissioners, employers, and patients can be assured that healthcare staff performing and/or interpreting diagnostic spirometry hold a valid, current certificate of competence.

Fractional exhaled nitric oxide (FeNO)

NICE produced diagnostics guidance on Measuring fractional exhaled nitric oxide concentration in asthma: NIOX MINO, NIOX VERO and NObreath in April 2014. FeNO devices are used for measuring the amount of nitric oxide in the breath. Nitric oxide is produced in the lungs, and increased levels of nitric oxide in the breath are thought to be related to lung inflammation and asthma. The draft clinical guideline acknowledges that FeNO challenge testing has only recently been introduced in primary care, and because of this the availability of FeNO testing equipment is patchy.

The project team contacted the manufacturers of the recommended devices (Circassia and Bedfont Scientific), who offered to supply a FeNO device and all consumables needed for the duration of the project to each site at no charge. Sites were given the manufacturer's contact details for both devices, and asked to follow their usual processes and considerations for choosing equipment to select the device they wished to use. Sites liaised directly with their chosen manufacturer to arrange delivery and training.

Peak flow

Peak expiratory flow (PEF) is an objective measure of lung function that has been widely used in the diagnosis and monitoring of asthma for many years. It is a measure of the maximum rate of expiration, generally expressed in litres/minute, and falls as the airways become narrowed because of bronchoconstriction. All sites were already measuring peak flow for some or all people with suspected asthma.

Direct bronchial challenge test with histamine and methacholine

Hyper-reactivity of the airways to non-specific stimuli (triggers) is a key feature of asthma. Bronchial hyper-reactivity (BHR) can be measured in a number of different ways. Inhalation of the bronchoconstrictors histamine and methacholine can be used to measure BHR. The draft clinical guideline acknowledged that the recommendations on bronchial challenge testing are a significant change to the diagnostic pathway. This test is only usually available in secondary and tertiary care, and it is likely only a few primary care professionals will have access to it on referral to secondary care at present. Sites were asked to note how many patients reached this point in the algorithms and what action they took.

Data collection

To establish the burden of asthma diagnosis in primary care, sites were asked to describe and record their existing pathway to diagnosis and to submit data for the equivalent 6-month calendar period in the previous year (May to October 2015). The baseline datasheet is shown in Appendix 1.

For the 6-month duration of the project (May to October 2016), sites were asked to implement the guideline and objective tests, follow the algorithms, and record the same information as was collected for the baseline. The metrics recorded during the 6-month project are shown in Appendix 2.

The project attempted to answer the following questions:

Question	Measure
Burden of asthma diagnosis to practices	• number of patients presenting to GP with asthma symptoms[1] • number of patients receiving an asthma diagnosis[1]

	• time spent on diagnosis appointments[1]
	• time from first presentation to diagnosis (including number of appointments)
	• for patients receiving an asthma diagnosis, the number diagnosed and their ages:
	  ○ in primary care
	  ○ after referral to secondary care
	  ○ during hospital admission.

Feasibility of introducing quality-assured spirometry into practice	• length of time to train practice staff to competency • type and grade of staff undertaking testing • time taken to undertake testing • clinic capacity needed • facilities needed • equipment cost • staff feedback
Feasibility of introducing FeNO into practice	• length of time to train practice staff to competency • type and grade of staff undertaking testing • time taken to undertake testing • clinic capacity needed • facilities needed • equipment cost • staff feedback
[1]6 months of project duration and 6-month equivalent calendar period in previous year	

Site monitoring and reporting arrangements

Sites were asked to submit data every month to the project team, using an excel spreadsheet on a secure site. Bi-monthly telephone calls were held to discuss progress and any issues, and a final site meeting was held to summarise and capture qualitative feedback.

During the 6-month delivery period of the project, sites were asked to:

- attend an initial face-to-face meeting with 2 members of the asthma feasibility project team, held at each practice

- attend bi-monthly semi-structured phone interviews with the asthma feasibility project team
- attend a final face-to-face meeting with 2 members of the asthma feasibility project team, held at each practice.

They were also asked to comment when the algorithm was not followed and give reasons for this.

At the final meeting, sites were asked 2 questions:

- Can the algorithm, as it currently stands, be implemented in a primary care setting?
- Would they continue with the algorithm if it remained unchanged at publication?

3. Stakeholder engagement

The asthma feasibility project team organised an update meeting for the stakeholders that were most active in providing consultation comments on the draft guideline. This meeting was held on 3 June 2016, and aimed to give stakeholders information about the projects' aims, objectives and progress. In all, 10 representatives attended from the following organisations: Association for Respiratory Technology & Physiology, Asthma UK, British Paediatric Respiratory Society, British Thoracic Society, Royal College of GPs, Royal College of Nursing, Royal College of Physicians. Apologies were received from: Association of Respiratory Nurse Specialists, Primary Care Respiratory Society UK, Royal College of Paediatrics and Child Health.

Thirteen stakeholders from the organisations listed above (apologies received from British Paediatric Respiratory Society and Royal College of Nursing) and 18 representatives from the participating sites attended a project closure meeting held on 21 December 2016. The aim of the meeting was to:

- give an overview of the high-level findings to representatives from the national organisations that were most active in providing consultation comments on the draft guideline

- provide the participating sites the opportunity to share their experiences of implementing the diagnostic algorithms with each other and with the invited stakeholders
- give stakeholder representatives an opportunity to ask questions of the sites involved in the project
- update the project sites and national stakeholder organisations about next steps.

4. Results

Demographic characteristics of the 7 project sites

The 7 project sites covered a total of 95,872 registered persons. Of these, 18,287 (19.1%) were under 18 (all England: 20.7%) and 16,570 (17.3%) were aged 65 or over (all England: 20.9%). The mean deprivation scale was 5 (SD 1.4) and 16,466 people (17.2%) were from non-white ethic groups. Table 1 gives a full breakdown of characteristics by project site.

Table 1: Demographic characteristics by project site

Site	Location of site (England)	Individual practices within site	Registered persons	% aged under 18	% aged 65 or over	Deprivation decile[1]	Ethnicit estimat % non-wh ethnic gro
1	East Midlands	3	14,120	21.9	18.4	6	6.6
2	East of England	4	17,500	15.9	29.1	6	1.1
3	London	1	7,302	15.1	6.0	6	36.0
4	North East	1	3,093	17.0	18.5	5	1.4
5	North West	2	10,985	18.2	3.6	2	46.5
6	South West	4	18,678	18.0	17.0	6	2.5
7	West Midlands	2	24,598	22.2	17.5	4	29.7

[1] Deprivation decile detailed on the National General Practice Profiles 2016 population tab for each practice. Taken from the Index of multiple deprivation score (IMD 2015). Scale 1-10. 1 = more deprived.
[2] Ethnicity estimate detailed on the National General Practice Profiles 2016 population tab for each practice. This is the estimated proportion of non-white ethnic groups in the practice population.

Baseline data

All sites stated that they would be able to provide baseline data in their project application. However, all sites struggled with identifying patients who had presented with 'suspected asthma'. While there is a read code for 'asthma suspected', sites reported this is rarely used in practice and so they had to rely on other codes and inhaler prescriptions without an asthma diagnosis to give them a 'proxy' estimation. Sites reported that this may be an overestimation of numbers of people actually presenting with suspected asthma. Two sites were unable to identify 'suspected asthma' cases with any accuracy, but all sites were able to identify those patients who had been coded as diagnosed with asthma in the baseline period.

All sites said they previously referred to BTS/SIGN guideline 141 on management of asthma (October 2014). For adults this recommends initial diagnosis based on a careful assessment of symptoms and a measure of airflow obstruction. In those patients with a high probability of asthma this included moving straight to a trial of treatment, with a recommendation for further testing for people whose response to a trial of treatment was poor.

All sites felt that a review of their baseline had been really helpful in focussing their efforts on improving the care pathway to diagnosis for their patients.

Project data

As the project information was being collected in real time, the accuracy of the data was superior to the retrospective baseline data. No proxy data was used by any site.

The ages of people on presentation are shown in Appendix 3 for both baseline and project data collection periods.

Burden of asthma diagnoses to practices

During the baseline period 42 new diagnoses of asthma were made compared with 35 during the project period. Table 2 shows the numbers presenting and the numbers diagnosed.

Table 2: Baseline and project suspected asthma and asthma diagnoses

		Baseline		Project		Comparison
Site	**Registered persons**	**Suspected asthma[1] (n)**	**Asthma diagnoses (n)**	**Suspected asthma (n)**	**Asthma diagnoses (n)**	**Change in number of asthma diagnoses (%)**
1	14,098	62	8	27	6	-25%
2	17,500	62	8	19	4	-50%
3	7,300	28	1	21	1	0
4[2]	3,074	8	2	15	7	+250%
5	10,900	30	1	18	2	+50%
6	19,000	N/A	7	19	7	0
7	24,000	N/A	15	24	8	-47%
TOTAL		**190**	**42**	**143**	**35**	**-17%**

[1] Proxy measure based on symptoms and prescribing. N/A = Not available

[2] Practice 4 employed an experienced part-time respiratory nurse between the baseline data period and project period

Across the 5 sites that were able to estimate full baseline data (sites 1–5), the number of people presenting with suspected asthma dropped from 190 to 100 in the baseline versus project period, but the percentage of asthma diagnoses increased from 11% to 20%, respectively. Across the 7 sites during the project period this proportion increased to 24.5% (35/143). In terms of overall numbers of asthma diagnoses, 3 sites decreased, 2 stayed the same and 2 increased, with a 17% decrease overall.

The dramatic increase in practice 4 was reported by the site to be because an experienced respiratory nurse practitioner had been taken on just before the project started. This practice had already identified asthma as a practice priority for improvement.

Because of the difficulty all sites experienced when gathering baseline data, and the approximate nature of this information, this cannot be considered an accurate reflection of the burden of asthma diagnosis before the project.

The mean number of days to diagnosis for the project, as shown in table 3, was greater than during the baseline period. This result is to be expected as all patients received an assessment appointment in the project period but this did not happen consistently during the baseline period.

Table 3: Time from presentation to asthma diagnosis

Period	Mean time to diagnosis (days)	Range (days)	Standard deviation
Baseline	35	0–128	31.7
Project	53	3–141	33.1

Figures 2 and 3 show the difference in number of appointments and number of days to reach an asthma diagnosis between the baseline and project periods achieved within the 6-month data collection periods. During the baseline period an asthma diagnosis was more likely to be made at first or second presentation than during the project period.

Figure 2: Number of appointments to asthma diagnosis

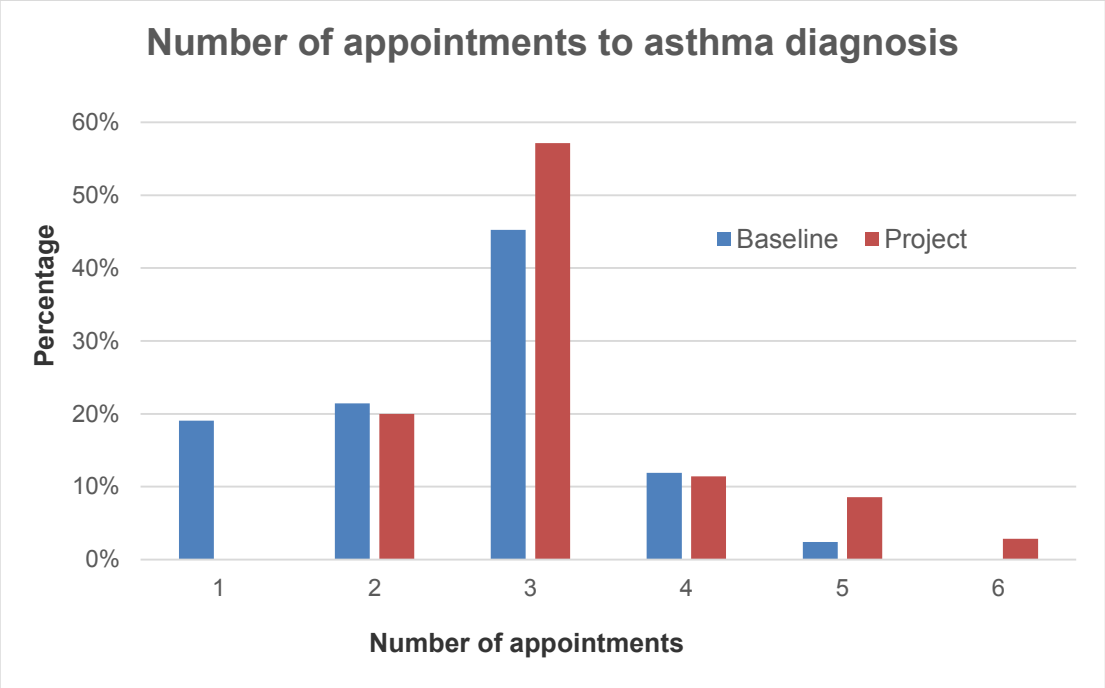
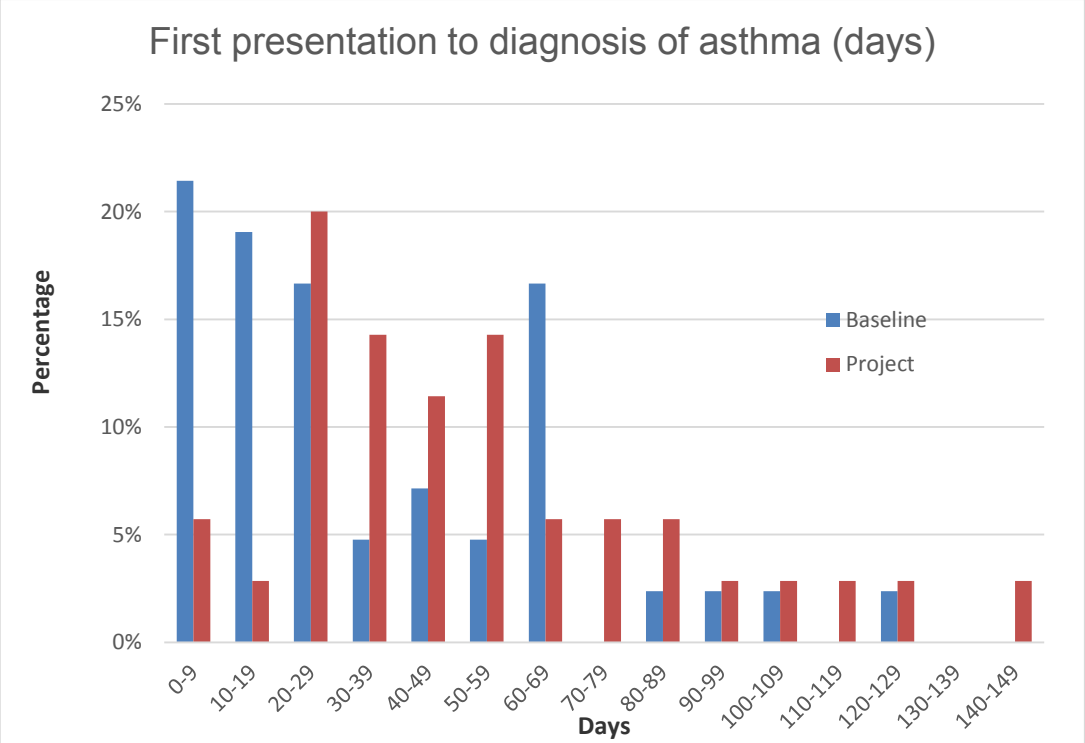


Figure 3: Time (number of days) from first presentation to asthma diagnosis



A further 11 people who had an ‘uncertain’ diagnosis at the end of the baseline period went on to be diagnosed with asthma at a later date. Their mean time to diagnosis was 219 days (range 20–379, SD 131).

Table 4 shows the diagnostic outcomes between the 5 sites that were able to identify people presenting with suspected asthma at baseline and all 7 sites for the project period.

Table 4: Diagnostic outcomes of people presenting with suspected asthma

	Baseline (5 sites)	**Project (7 sites)**
Asthma	20 (10.5%)	35 (24.5%)
Other	35 (18.4%)	19 (16.1%)
Uncertain	135 (71.1%)	85 (59.4%)
Total	190	143

Practices reported a higher level of confidence in the diagnosis of asthma during the project period. The project data may also reflect that GPs gave more thought to who they referred as 'suspected asthma' for diagnostic testing and assessment by the practice nurse.

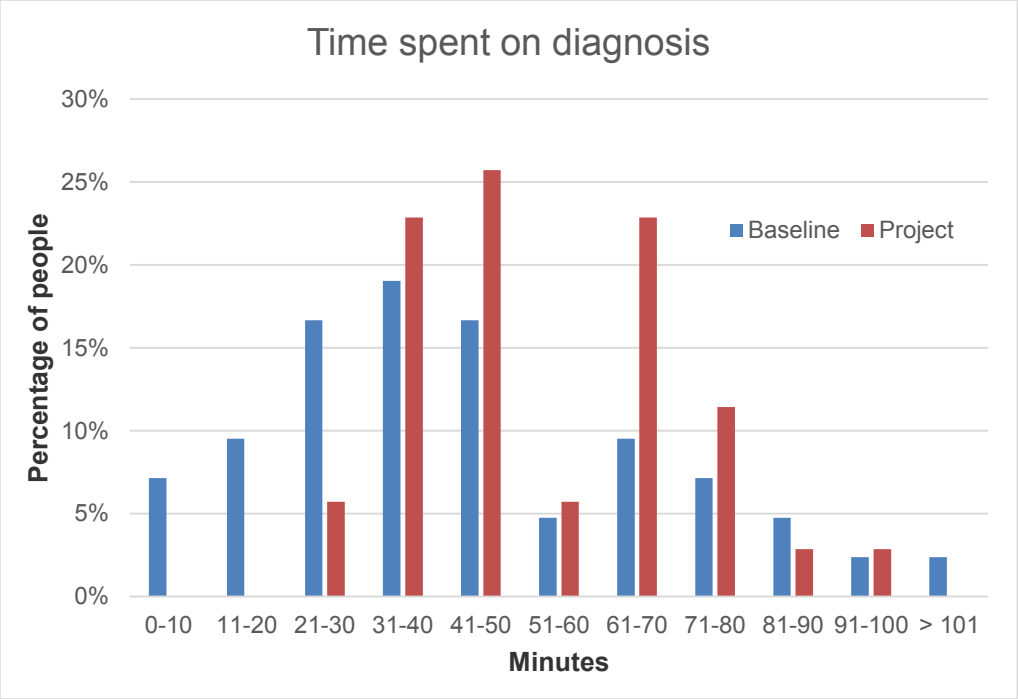
During the project data collection period, of the 85 patients that were classed as 'uncertain' at the end of the data collection period:

- 32 (37.6%) had not yet completed the algorithm (for example, they had not yet had a follow-up appointment after the diagnostic tests)
- 25 (29.4%) failed to attend for follow-up; for 16 of the 25 (64%) this was after receiving a peak flow diary
- 28 (32.9%) had completed the algorithm and attended all appointments but the clinician was still uncertain of the final diagnosis.

Time taken for assessment

Sites were asked to identify the total time spent on appointments to reach an asthma diagnosis at baseline and during the project. Figure 4 shows the range across all patients. The average time to reach a diagnosis rose from 49 minutes (range 10–140, SD 27) during the baseline period to 57 minutes (range 30–100, SD 18) during the project. This result reflects that all patients received a diagnostic assessment appointment within the project period.

Figure 4: Time spent on diagnosis appointments (including initial presentation appointment) all sites



Time allocated to asthma assessment varied between sites both before and during the project, as shown in table 5. This also reflects the variation during the project shown in figure 4.

Table 5: Time allocated for asthma assessment appointments following initial presentation appointment (by site)

Site	Baseline[1]	Project	
		Spirometry and FeNO	BDR
1	10 mins GP, 2 x 20 mins nurse	60 mins nurse	
2	30–40 mins nurse	70 mins nurse	
3	2 x 15 mins nurse	15 mins nurse	15 mins nurse
4	20 mins nurse	40 mins nurse	
5	2 x 20 mins nurse	20 mins nurse	20 mins nurse
6	30 mins nurse	30 mins nurse	
7	2 x 30 mins nurse	30 mins nurse	30 mins nurse

[1] During the baseline all sites reported that not all patients followed this pathway, with many not receiving a referral for a nurse assessment.

The methods used for allocating diagnostic assessment appointments varied. Some practices already had nurse-led respiratory clinics that had been set up before the project, and used these. Others set up clinics as part of implementing the project. Some sites allocated routine slots into practice nurse sessions. Two sites also used

healthcare assistants to undertake the spirometry and FeNO testing, and 1 site is planning to do this.

The interpretation of test results was done by the nurses at all but 1 site, which sent results to the GP for final interpretation.

Three sites took the opportunity to redesign their asthma appointments before the project started, allocating more time to the nurse assessment appointment. These sites felt that spending more time on assessment would prevent future 'revolving door' presentations with the GP.

Some sites reported high non-attendance rates for the assessment appointments, particularly if the person's symptoms had improved with use of an inhaler.

Spirometry

Training and competency

At baseline, 6 out of 7 sites had nurses who already did spirometry as a routine part of their asthma diagnosis pathway, and all sites used spirometry to diagnose chronic obstructive pulmonary disease (COPD).

Of the 7 sites, 3 already had staff fully certified in spirometry. Five sites attempted to access ARTP-accredited spirometry training in the 6-month project timescale:

- One site chose an Education for Health level 5 module in performing quality-assured spirometry for 2 practice nurses (£598 per person). This involved 4 months e-learning and attendance at 1 study day and 1 assessment day leading to foundation level entry on the ARTP national register.
- Two sites accessed classroom based ARTP accredited performance and interpretation training (2 day course):
  - 1 site accessed local training for 2 GPs and a practice nurse (course fee £250 per person)
  - 1 site could only access training 350 miles away, meaning 2 nurses had to take 2 additional days out of work time for travel (course fee £200 per person, plus £200 per person for full certification).
- Two sites could not access any ARTP training locally:

- 1 site opted for ARTP e-learning for a GP and practice nurse (course fee £275 per person)
- 1 site opted for non-ARTP local public health team spirometry training for their healthcare assistant (free of charge).

All sites commented that spirometry testing can be difficult because of the time practitioners and patients need to perform it correctly. Sites were made aware by the project team of the recently published competency assessment framework for diagnostic spirometry, and had questions about how this was going to be implemented and monitored.

Sites agreed that spirometry should be improved and quality assured and reflected that the competency assessment seemed a good initiative that should be implemented. They also indicated that many practices may struggle to achieve this, creating a major adoption challenge. They also all agreed that there are patient-related motivational, comprehension and cultural issues in getting this right, and that these all present potential adoption challenges.

It should be noted that the challenges facing quality-assured diagnostic spirometry would also apply to a number of other conditions, most notably COPD.

The classroom-based ARTP training received by 2 sites (2-day course for performing and interpreting) was reported as being really helpful, with participants saying they learnt a lot that would improve their practice. Only 2 nurses (from the same site) opted to register for full certification (completion of a portfolio, an assignment, a practical and oral exam). This was reported to be time consuming and difficult (but worthwhile) by certified staff at other sites, and a barrier to implementing the NICE guideline by other non-certified staff. Sites suggested that the training should be given by practitioners with experience of working in a primary care setting. Feedback from training given in secondary and tertiary centres was that this did not necessarily meet the needs of a primary care audience.

The ARTP also offer an experienced practitioner scheme for people who are already highly experienced at performing spirometry so do not need further training/experience. Candidates have to meet stringent criteria to be eligible for the

scheme, and if suitable can take a practical assessment to obtain the Foundation or Full Certificate.

Spirometry outcomes in project period

Of the 143 people who presented with suspected asthma during the project period, algorithms were started in 137 people (the remaining 6 people were still awaiting the diagnostic assessment appointment at the end of the project). Table 6 shows the spirometry outcome results during this time.

Table 6: Spirometry results for all people during the project period

Status	All people	People diagnosed with asthma
Assessment completed	137/143	35/137
Spirometry successfully completed	124/137 (90.5%)	33/35 (94.2%)
Person not able to do spirometry	9/137 (6.6%)	1/35 (2.9%)
Spirometry contraindicated	4/137 (2.9%)	1/35 (2.9%)
Spirometry result normal	102/124 (82.3%) of completed	24/33 (72.7%) of completed
Spirometry result obstructive	22/124 (17.7%) of completed	9/33 (27.3%) of completed

All clinicians involved commented that because of the nature of the disease, spirometry may not pick up airway obstruction as this only happens if the person is symptomatic at the time of testing. Of the 33 people diagnosed with asthma during the project, whose spirometry was successfully completed, only 9 had an obstructive result.

Some nurses continued to do bronchodilator reversibility testing for patients with suspected asthma who had a lower than expected spirometry result that was still classed as ‘normal’ by the algorithm.

One site was sceptical about the use of spirometry to diagnose asthma, and did not change their view as a result of completing the project.

Two sites commented that the guideline does not make allowances for patients who are unable to perform, or are contraindicated for, the diagnostic tests. While this may be a relatively small proportion of people with suspected asthma (2.9% in the project), it could work out to be a significant number nationally.

All sites commented on the difficulty of performing spirometry on very young children, and many commented that they thought the diagnostic algorithm for children should be for those aged 8 years and over. During the project period 6 children (4.2%) aged 5 to 7 years presented with asthma symptoms. Two of these children were unable to perform spirometry, and 1 child (aged 5) could not perform either spirometry or FeNO.

FeNO

None of the sites had any previous experience of using a FeNO device and all 7 were keen to try it: 5 sites opted to use the NIOX VERO device and 2 sites chose the NObreath device. All sites reported that the devices and consumables are expensive, and that widescale adoption is unlikely to occur without financial incentive. CCG bulk buying of spirometers and point-of-care coagulometers were cited as examples of how this might be achieved.

All sites received training from the manufacturer on use of the device and how to interpret results. There is no formal assessment of competency for the use of the FeNO devices, but this was reported to be straightforward by the sites and training took less than 1 hour. Sites felt that an improved knowledge and understanding of the FeNO test and results would be necessary if this test becomes part of routine practice in asthma diagnosis.

Six sites stated that FeNO was a welcome addition to the diagnostic process and an easy test to carry out, with positive feedback from patients. It was also reported that using FeNO gives additional confidence in prescribing decisions at an earlier stage.

One site suggested that FeNO should be the first-line test as it is easier to perform than spirometry. People who failed to successfully complete spirometry and FeNO, may have been able to complete the FeNO if this had been the first-line test due to the effort involved in performing spirometry.

The read code some practices used to record the test is XaRCB (exhaled nitric oxide test). The result was then written in a free text box on the electronic patient record and an explanation given if necessary. The clinicians involved in the project thought that, as FeNO is a new test to general practice, it was important to record and explain test results for other members of staff.

Sites were concerned about the accuracy and usefulness of FeNO in people who smoke. It was reported that the manufacturers advise patients to not smoke for 48 hours before the test, as smoking can depress FeNO levels. Sites reported poor patient compliance with this. This may present a significant adoption issue for this group of patients.

Opinions on FeNO differed between the practices depending on the particular FeNO device used. Positive factors included high patient acceptance and aiding patient motivation and better clinician confidence in terms of prescribing decisions. Device issues raised included time to start up and calibrate between readings, subjectivity in performing the test and interpreting the result, a result being provided regardless of whether the test was carried out correctly or not, and results not being integrated into the practice system.

One site reported persistent operational problems that affected test results, meaning they were not consistent or reproducible. This site also reported that their device made an unacceptably loud noise during operation and the manufacturer performed a modification to reduce this. Because of these issues, they had little confidence in the use of FeNO in the diagnostic pathway.

A number of sites suggested that a 'hub and spoke' model for asthma diagnosis may improve the feasibility of widescale FeNO adoption as it would enable better use of resources.

Peak flow

Issues with peak flow diaries were patient compliance and non-attendance at follow-up. This was reported to be an issue both before and during the project. One practice suggested that it may be better to give the peak flow diary to the patient at presentation so that this could be monitored throughout the acute and recovery phases. This may also shorten the time to diagnosis and reduce the likelihood of non-attendance. If a patient does not return to the practice with their peak flow diary for the final appointment the algorithm cannot be completed, creating a significant implementation issue. Of the 90 people who were supposed to return with a completed peak flow diary before the end of the project period, 18 (20%) did not attend and a further 6 (7%) did not complete the algorithm.

Direct bronchial challenge testing

All sites reported that the algorithm comes to a dead end at direct bronchial challenge testing with histamine or methacholine. No sites were able to refer people for this test, as it was not available in their local secondary care respiratory clinic. During the project 14 people came to this point in the algorithm. Four people were referred for a secondary care outpatient appointment as the only alternative option available, and have not yet received a diagnosis. Of the other 10 people kept in primary care, 4 were diagnosed with asthma following a trial of treatment and 6 were 'other' or 'uncertain' by the end of the project period.

Other diagnosis data

During the baseline period, 90.5% (38/42) of people received their asthma diagnosis in primary care. During the project period all asthma diagnoses were made in primary care.

The approach to formally diagnosing patients and coding this on IT systems during the project period varied between practices. At 3 sites GPs took responsibility for doing this. At the other 4 sites the nurses carrying out the diagnostic algorithm generally diagnosed and recorded the outcome. Two sites reported that nurses may not have the autonomy or feel comfortable diagnosing patients, and that the reason for this may be that diagnosis is a fairly new area of practice for some nurses.

Adherence to draft guideline algorithms

During the project data collection period, 137 people attended an asthma assessment appointment. The remaining 6 people were waiting for an assessment appointment at the end of October 2016.

The algorithm was followed exactly in 75 people (54.7%), with the remaining 62 people (45.3%) experiencing deviations from the algorithms because of either their ability to complete the tests (10) or alternative clinical judgement (52).

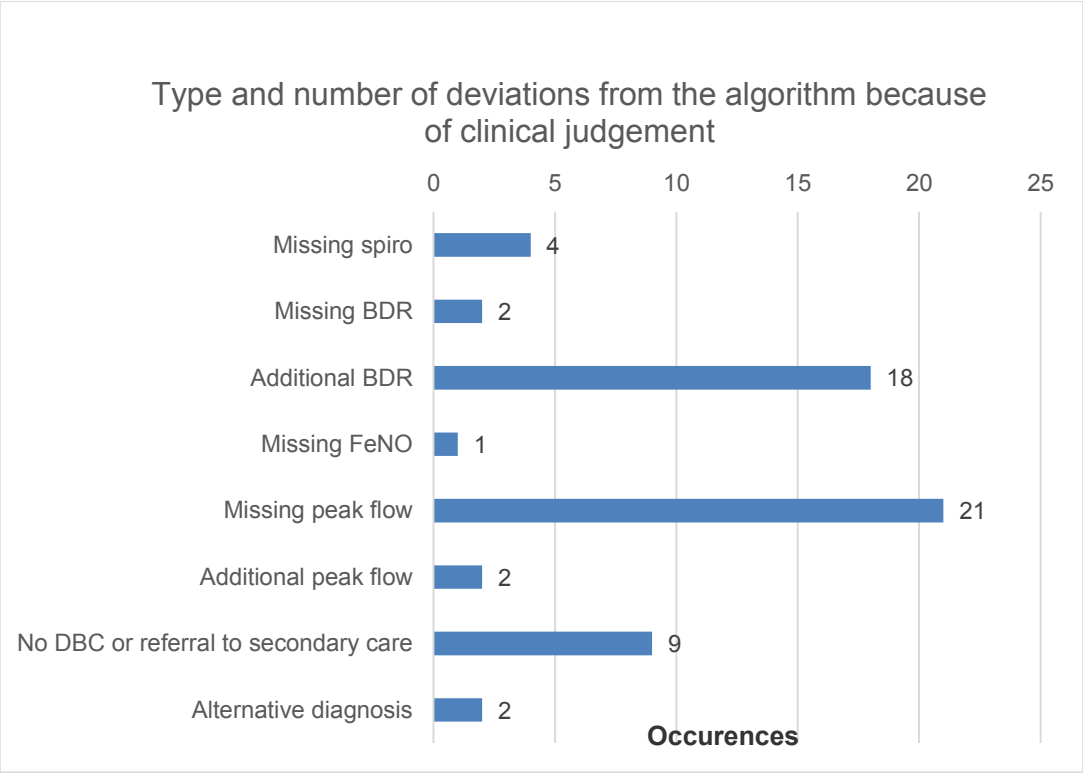
Of the 10 patients who were unable to complete the diagnostic tests:

- 5 were unable to do spirometry
- 1 was unable to do FeNO
- 4 were unable to do either spirometry or FeNO.

Reasons given were: too difficult (5 children, 3 adults) and issues with language barriers making it difficult to explain what to do (2).

For the remaining 52 patients, clinical judgement was the reason given for deviating from the algorithm (see figure 5).

Figure 5: Deviations from algorithm



Site conclusions

All sites agreed that the algorithm could be implemented into primary care as it stands, and that implementation is not an overwhelming burden for those patients who were already being referred appropriately for spirometry assessment by the practice nurse. All sites acknowledged that collecting the baseline data highlighted that, previous to the project, some patients were just being seen by the GP, given a beta$_2$ agonist inhaler and then not followed up. All sites reported that this was not their agreed pathway before the project and was not good practice.

All sites felt the algorithms were too busy, and the text sixe too small, making them difficult to use in clinics because of a lack of space to display them. Lack of familiarity with the algorithms was also raised as an issue, particularly if they were not being used every day. One site suggested merging the adult algorithms onto 1 page (normal and obstructive).

All sites stated that doing diagnostic testing with small children is very difficult. They considered a more reasonable age to attempt diagnostic testing to be 8 years and over.

Of the 7 sites, 6 said they would like to continue with the algorithm if it remained unchanged at publication. However all sites stated that this was helped by being given the FeNO device free of charge by the manufacturer. Reasons given were that the algorithms had improved time to diagnosis and confidence in diagnosis. The increased confidence came from the addition of the quantitative element to diagnosis and the avoidance of diagnosis at initial presentation.

One site is trying to gain partner agreement to continue using FeNO because of the ongoing cost of consumables.

The site that said they would not continue with the algorithm said they would revert to previous practice and did not find either the spirometry or FeNO testing particularly useful for asthma diagnosis.

5. Implementation levers

The following implementation/adoption levers were identified.

All practices reported that being part of the project has ensured that GPs have consistently referred patients with suspected asthma to the practice nurse for assessment, and that this is a great improvement on previous practice. Sites feel that this has helped prevent ‘revolving door patients’. These are people who present with symptoms, are given an inhaler, and then not followed up or coded as suspected asthma. These patients may re-present to a GP during exacerbations on a number of occasions without receiving a formal diagnosis.

A number of sites commented that any increased time for assessment is offset by saving GP time with these patients in the future.

One site reported that, as a result of implementation of the algorithms, there are now fewer people being prescribed inhalers without a diagnosis. This same site indicated that they now start fewer people on $beta_2$ agonist inhalers.

Referral to a practice nurse for assessment and advice was not happening consistently at any site before the project. Some sites commented that adding structure to the diagnostic process had really helped improve consistency.

6. Project team reflections

If this project were to be repeated, competency with diagnostic spirometry would have to be established in line with the new recommendations from NHS England. This would likely make site recruitment more challenging, as only practices with appropriately certified staff could legitimately attempt implementation of the guideline. By default, this will also make real-world implementation of the guideline more challenging than has been reported here.

A key issue highlighted by sites was the confusion and disconnect in user understanding of the differences, overlap, benefits and drawbacks of having 2 sets of nationally-produced guidelines on diagnosing asthma, especially as they had conflicting advice. The project team were able to explain the different methodologies to the sites, and in particular the fact that NICE consider cost effectiveness as well as evidence of clinical effectiveness in developing guideline recommendations. All sites said they were unaware of these differences. An implementation aid to support uptake of this guideline could include a comparison of the scope, design and methods employed by different guideline developers or an annotated version explaining the rationale for differences to reduce user confusion.

Part of the selection criteria for site recruitment was the ability to provide baseline data. This may have put off some sites who had considered applying, particularly if they had already identified how complex this could be to do. This information has highlighted that being able to measure local success associated with implementing the guideline, using before and after data, could be a more commonplace barrier to implementation than previously thought. If the same project were to be delivered again, collecting real time data before and during the project would improve the accuracy of comparisons. Improvements in accurately coding for asthma are needed to allow for data collection and measuring local impact.

7. Summary and conclusions

This feasibility project set out to evaluate if the diagnostic elements of the draft asthma diagnosis and monitoring guideline could be implemented into practice in primary care, in response to concerns raised during guideline consultation.

The draft NICE guideline published in January 2015 identified that the 3 most important and challenging areas to adopt will be:

1 using spirometry

2 FeNO challenge testing

bronchial challenge testing.

In all, 7 sites implemented the diagnostic algorithms, collected data for comparison and reported back on their implementation experience. The findings identified in this work are summarised below:

Algorithms

- the diagnostic algorithms can be implemented into practice
- 5 out of 7 sites would continue to use the algorithms if the guideline were published as it is
- the algorithms could benefit from simplification
- the algorithms are impractical for many children under 8
- the recommendations do not cover what to do with patients who are contraindicated/unable to undergo diagnostic testing

Spirometry

- diagnostic spirometry takes time to do correctly
- the new competency recommendations create adoption issues around access to (and funding of) training but the importance of improving the quality assurance of spirometry nationally was recognised both for asthma and other respiratory conditions
- there is scepticism with spirometry picking up airway obstruction, as this only happens if the person is symptomatic at the time of testing

FeNO

- the cost of FeNO devices and consumables is a barrier to implementation
- positive clinician feedback and high patient acceptance with FeNO may act as a lever
- lack of clinician confidence in specific FeNO devices to produce consistent results may present an adoption issue

Other

- bronchial challenge testing is largely not available in secondary care making it difficult to refer patients for this when they reach the relevant part of the algorithm
- patient acceptance and compliance present challenges in the clinician's ability to complete the full care pathway, for example:
    - poor completion of peak flow diaries
    - failure to abstain from smoking for 48 hours before tests
    - failing to attend follow-up appointments (clinicians felt attendance was driven by patient symptoms)
- conflicting national guidelines on diagnosing asthma may present implementation issues.

The commissioning of this project demonstrates commitment and responsiveness on behalf of the guideline developers to explore concerns raised during consultation about its implementation. This is consistent with NICE's wider accountability objectives. While this project has demonstrated the guideline can be implemented into practice, and will be by some, others may feel that in the current NHS climate the barriers identified will prevent them from doing so.

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Sites involved in the development of this report have received training, equipment and consumables free of charge from the 2 companies that provide NICE-recommended FeNO technologies. The content of this report has been checked for factual accuracy, to ensure it is fair and balanced, and to ensure its compliance with appropriate regulations.

3. *Appendix 1*

ASTHMA FEASIBILITY PROJECT BASELINE DATA

TO BE COMPLETED FOR ALL PEOPLE PRESENTING WITH SUSPECTED ASTHMA MAY - OCTOBER 2015									
Patient	Date of presentation	Age	Final diagnosis*	Date of asthma diagnosis	Time spent on diagnosis appointments (minutes)	Number of appointments to diagnosis	Place of diagnosis#	Practice	Comment
1									
2									
3									
4									
5									
6									

* asthma/other/uncertain

primary care/secondary care OPD/secondary care admission

Appendix 2

ASTHMA FEASIBILITY PROJECT METRICS

Presentation

- Date
- Age
- Appointment duration (minutes)

Spirometry

- Spirometry date
- Appointment duration (minutes)
- Spirometry result (obstructive/normal)
- Number of filters used
- Staff performing spirometry (HCA/nurse/GP)
- Staff interpreting spirometry (HCA/nurse/GP)

Bronchodilator reversibility (BDR)

- BDR test date
- Appointment duration (minutes)
- BDR result (positive/negative/N/A)
- Number of filters used
- Staff performing BDR(HCA/nurse/GP)
- Staff interpreting BDR (HCA/nurse/GP)

FeNO

- FeNO date
- Appointment duration (minutes)
- FeNo result (positive/negative/N/A)
- Number of filters used
- Staff performing FeNo (HCA/nurse/GP)
- Staff interpreting FeNo (HCA/nurse/GP)

Peak flow variability

- Peak flow variability monitored (Yes/No)
- Peak flow result (positive/negative/N/A)

Direct bronchial challenge

- Date referred for direct bronchial challenge test
- Date of test
- Bronchial challenge test result (positive/negative/N/A)

Other onward referral

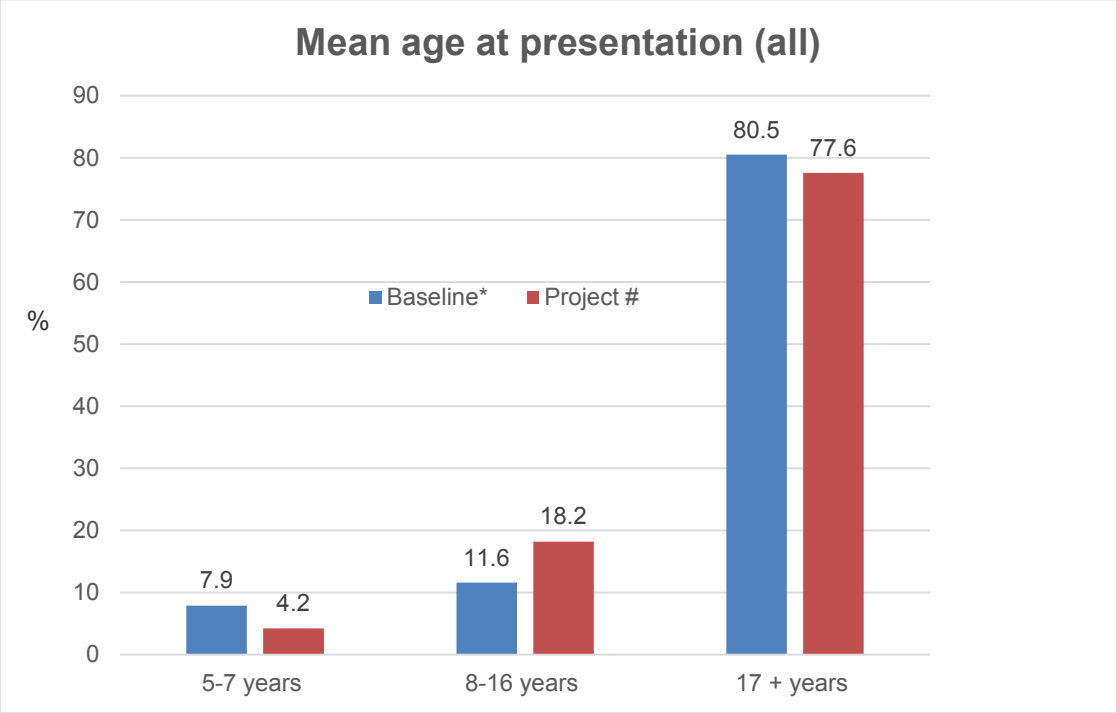
- Other onward referral (Yes/No)
- Referred to

Diagnosis

- Date of diagnosis
- Diagnosis (Asthma/Other/Uncertain)
- Diagnosing clinician (Site nurse/Site GP/Secondary care)
- No. of practice appointments to reach diagnosis

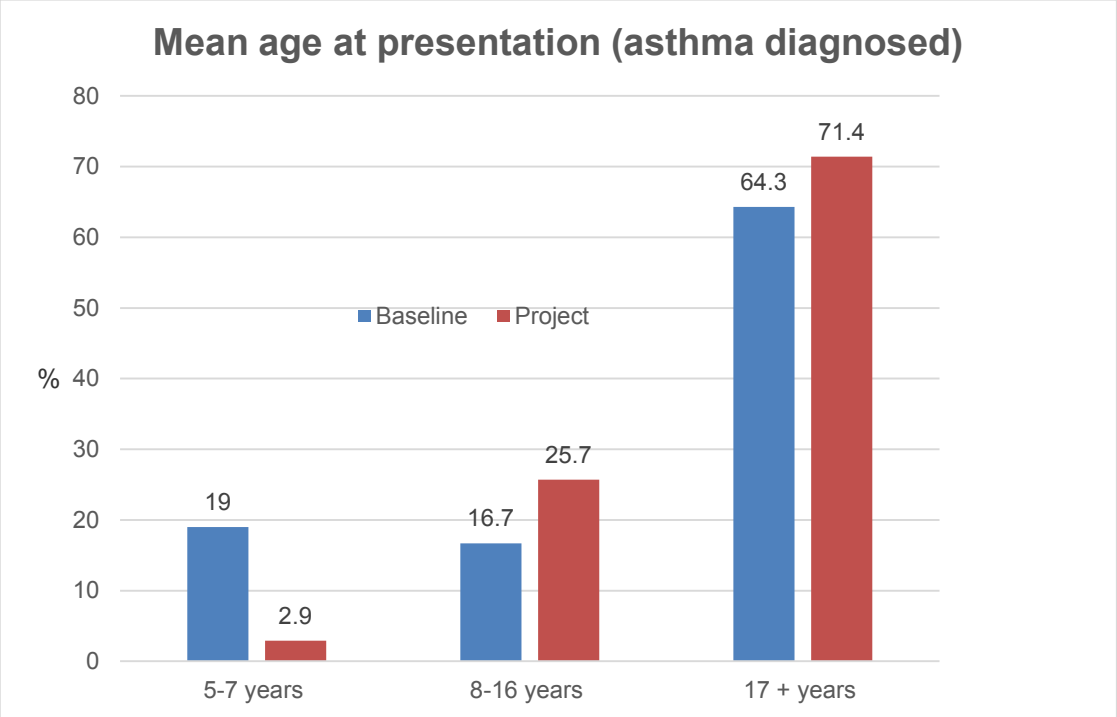
Appendix 3

Age of people on presentation with suspected asthma



* Baseline: 5 sites. # Project: 7 sites.

Age of people on presentation who were diagnosed with asthma



Data shown for all sites for baseline and project.

Appendix R: Summary of evidence from 2017 updated searches for Asthma: diagnosis and monitoring

Appendix R: Summary of evidence from 2017 updated searches for Asthma: diagnosis and monitoring

Summary of evidence

Diagnosis: Signs and symptoms

Q – 01 In people under investigation for asthma, what is the diagnostic accuracy of each of the following signs and symptoms: wheezing, cough, breathlessness, nocturnal symptoms, diurnal and seasonal variations?

Recommendations derived from this question

Initial clinical assessment

1. Treat people who are acutely unwell at presentation immediately, without delaying for objective tests.
2. Perform objective tests at the time of presentation (including spirometry and FeNO) whenever possible. If objective tests cannot be done immediately, they should be done when acute symptoms have been controlled.
3. Do not make a formal diagnosis of asthma until objective tests have been done.

Signs and symptoms

4. Take a structured clinical history in people with suspected asthma. Specifically, check for:
   - wheeze
   - cough
   - breathlessness
   - any variation in the above symptoms occurring over the course of 24 hours or seasonally.
5. Do not use symptoms alone without an objective test to diagnose asthma. See also recommendation 27.
6. Physically examine people with suspected asthma to identify expiratory polyphonic wheeze and signs of other causes of respiratory symptoms, but be aware that even if examination results are normal the person may still have asthma.

Update decision

No new information was identified.

Initial clinical assessment

Update summary

No relevant evidence was identified.

Committee feedback

No Committee feedback was relevant to this evidence.

Page 1 of 20

Signs and symptoms

Update summary

No relevant evidence was identified.

Committee feedback

No Committee feedback was relevant to this evidence.

Q – 02 In people under investigation for asthma, what is the diagnostic accuracy of taking a personal/family history of atopic disorders?

Recommendations derived from this question

7. Ask about a personal or family history of atopic disorders. Record any triggers that make symptoms worse.
8. Do not use a history of atopic disorders alone to diagnose asthma.

Update decision

No new information was identified.

Taking personal/family history

Update summary

No relevant evidence was identified.

Committee feedback

No Committee feedback was relevant to this evidence.

Q – 03 In people under investigation for asthma, what is the diagnostic accuracy of a clinical history of symptoms in response to exercise?

Recommendations derived from this question

9. Do not use an isolated clinical history of symptoms after exercise to diagnose asthma.

Update decision

No new information was identified.

Clinical history of symptoms in response to exercise

Update summary

No relevant evidence was identified.

Committee feedback

No committee feedback was relevant to this evidence.

Q – 04 In people under investigation for asthma, what is the diagnostic accuracy of a clinical history of symptoms after taking the following drugs: in adults (beta blockers, aspirin, or other NSAIDs) or in children (ibuprofen)?

Recommendations derived from this question

No clinical recommendations.

Update decision

No new information was identified.

Clinical history of symptoms after taking medication in adults

Update summary

No relevant evidence was identified.

Committee feedback

No Committee feedback was relevant to this evidence.

Clinical history of symptoms after taking medication in children

Update summary

No relevant evidence was identified.

Committee feedback

No Committee feedback was relevant to this evidence

Q – 05 In adults under investigation for occupational asthma, what is the diagnostic accuracy for case identification, of asking whether their symptoms are better away from work?

Recommendations derived from this question

10. Check for suspected occupational asthma by asking employed people with newly-diagnosed asthma or established asthma that is poorly controlled:
    - are symptoms better on days away from work?
    - are symptoms better when on holiday[1]?

    Make sure all answers are recorded for later review.
11. Refer people with suspected occupational asthma to an occupational asthma specialist.

[1] 'Holiday' here means any longer time away from work than usual breaks at weekends or between shifts.

Update decision

No new information was identified.

Case identification

Update summary

No relevant evidence was identified.

Committee feedback

No Committee feedback was relevant to this evidence

Symptoms when away from work

Update summary

No relevant evidence was identified.

Committee feedback

No Committee feedback was relevant to this evidence

Q – 06 In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of spirometry/flow volume loop measures?

Recommendations derived from this question

12. Use spirometry as the first investigation for asthma in adults and young people older than 16 and children aged 5-16 years. Regard a forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio of less than 70%[2] as a positive test for obstructive airway disease (obstructive spirometry). See also recommendation 28.

Update decision

No new information was identified.

---

[2] Or the lower limit of normal if the calculation is available for children aged 5-16 years.

Spirometry/flow volume loop measures

Update summary

No relevant evidence was identified.

Committee feedback

No Committee feedback was relevant to this evidence

Q – 07 In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of bronchodilator response (using PEF or FEV1)?

Recommendations derived from this question

13. Offer a bronchodilator reversibility (BDR) test to adults and young people older than 16 with obstructive spirometry (FEV_1/FVC ratio less than 70%). Regard an improvement in FEV_1 of 12% or more, together with an increase in volume of 200 ml or more, as a positive test.

14. Consider a BDR test in children aged 5-16 years with obstructive spirometry (FEV_1/FVC ratio less than 70%). Regard an improvement in FEV_1 of 12%[3] or more as a positive test.

Update decision

No new information was identified.

---

[3] Or the lower limit of normal if the calculation is available for children aged 5-16 years.

Bronchodilator response

Update summary

No relevant evidence was identified.

Committee feedback

No Committee feedback was relevant to this evidence

Q – 08 In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of peak expiratory flow (PEF) variability?

Recommendations derived from this question

15. Monitor peak flow variability for 2-4 weeks in adults and young people older than 16 if there is diagnostic uncertainty after initial assessment and they have either:
    - normal spirometry and the results of a fractional exhaled nitric oxide (FeNO) test or
    - obstructive spirometry, reversible airways obstruction (positive BDR) and a FeNO level of 39 parts per billion (ppb) or less.

    Regard a value of more than 20% variability as a positive test.

16. Consider monitoring peak flow variability for 2-4 weeks in adults and young people older than 16 if there is diagnostic uncertainty after initial assessment and they have:
    - obstructive spirometry **and**
    - irreversible airways obstruction (negative BDR) **and**
    - a FeNO level between 25 and 39 ppb.

    Regard a value of more than 20% variability as a positive test.

17. Monitor peak flow variability for 2-4 weeks in children aged 5-16 years if there is diagnostic uncertainty after initial assessment and they have either:
    - normal spirometry and the results of a FeNO test **or**
    - obstructive spirometry, irreversible airways obstruction (negative BDR) and a FeNO level of 35 ppb or more.

    Regard a value of more than 20% variability as a positive test.

Update decision

No new information was identified.

Peak expiratory flow (PEF) variability

Update summary

No relevant evidence was identified.

Committee feedback

No Committee feedback was relevant to this evidence

Q – 09 In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of skin prick tests?

Recommendations derived from this question

Please see next question.

Update decision

No new information was identified.

Skin prick test

Update summary

No relevant evidence was identified.

Committee feedback

No Committee feedback was relevant to this evidence.

Q – 10 In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of total and specific serum IgE measures?

Recommendations derived from this question

18. Do not offer the following as diagnostic tests for asthma:
    - skin prick tests to aeroallergens
    - serum total and specific IgE.
19. Be aware that skin prick tests to aeroallergens or specific IgE tests may be used to identify triggers after a formal diagnosis of asthma has been made.

Update decision

No new information was identified.

Specific serum IgE-measures

Update summary

No relevant evidence was identified.

Committee feedback

No Committee feedback was relevant to this evidence.

Q – 11 In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of fractional exhaled nitric oxide (FeNO) measures?

Recommendations derived from this question

20. Be aware that a person's current smoking status can lower FeNO levels both acutely and cumulatively.

21. Offer a FeNO test to adults and young people older than 16 if a diagnosis of asthma is being considered. Regard a FeNO level of 40 parts per billion (ppb) or more as a positive test.

22. Consider a FeNO[4] test in children aged 5–16 years if there is diagnostic uncertainty after initial assessment and they have either:
    - normal spirometry or
    - obstructive spirometry with negative BDR.

    Regard a FeNO level of 35 ppb or more as a positive test.

Update decision

This review question should not be updated.

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[4] Children at the lower end of the age range may not be able to do the FeNO test adequately. In these cases, apply the principles in recommendation 27.

Diagnostic test accuracy of FeNO for the diagnosis of asthma

Update summary

A study[8] in 923 patients with suspected asthma assessed the diagnostic accuracy of FeNO to confirm or rule out asthma. The definite diagnosis of asthma was based on a positive bronchodilation or bronchoprovocation test result. All patients underwent both the index test and reference standard. FeNO levels were significantly higher in asthmatics than in non-asthmatics regardless of whether the asthma diagnosis was established using the bronchoprovocation or bronchodilation test. In patients with a positive bronchoprovocation test, the best cut-off value of FeNO to identify asthma was 64ppb with a sensitivity of 52% and a specificity of 94.35%. In patients with a positive bronchodilation test, the best FeNo cut-off value was 41ppb with a sensitivity and specificity of 72.43% and 74.85%, respectively. The study also considered the influence of smoking history on FeNO levels. FeNO levels were significantly lower in men with a positive smoking history compared to men without any history of smoking (34.2ppb versus 43.6ppb, p=0.001). There was no significant difference in FeNO levels based on smoking history in women (34.2ppb versus 31.5ppb, p=0.558).

Committee feedback

No Committee feedback was relevant to this evidence.

New evidence is unlikely to change guideline recommendations.

Q – 12 In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of eosinophil blood count measures?

Recommendations derived from this question

23. Do not offer a peripheral blood eosinophil count as a diagnostic test for asthma.

Update decision

No new information was identified.

Eosinophil blood count measures

Update summary

No relevant evidence was identified.

Committee feedback

No Committee feedback was relevant to this evidence

Q – 13 In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of airway hyper-reactivity (non-specific bronchial challenge) with histamine and methacholine?

Recommendations derived from this question

24. Offer a direct bronchial challenge test with histamine or methacholine[5] to adults and young people older than 16 if there is diagnostic uncertainty after a normal spirometry and either a:
    - FeNO level of 40 ppb or more and no variability in peak flow readings **or**
    - FeNO level of 39 ppb or less with variability in peak flow readings.

    Regard a PC20 value of 8 mg/ml or less as a positive test.

25. Consider a direct bronchial challenge test with histamine or methacholine[5] in adults and young people older than 16 with:
    - obstructive spirometry **and**
    - a FeNO level between 25 and 39 ppb **and**
    - no variability in peak flow readings (less than 20% variability over a 2-4 week period).

    Regard a PC20 value of 8 mg/ml or less as a positive test.

Update decision

No new information was identified.

[5] At the time of interim publication (January 2016), histamine and methacholine did not have UK marketing authorisation for this use. The healthcare professional should follow relevant professional guidance, taking full responsibility for the decision to use this test. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

Q – 14 In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of airway hyper-reactivity (non-specific bronchial challenge) with mannitol?

Recommendations derived from this question

No clinical recommendations.

Update decision

This review question should not be updated.

Diagnostic test accuracy of a mannitol challenge test

Update summary

One cross-sectional study[5] including 88 adults with asthma-related symptoms but no prior diagnosis of asthma was identified. The study evaluated the diagnostic accuracy of a mannitol challenge test. A diagnosis of asthma was made based on clinical symptoms and reversible airflow obstruction. The mannitol challenge test was considered positive if there was a 15% fall in FEV1. Sixty-seven of the 88 patients received a definite diagnosis of asthma. The mannitol challenge test had a sensitivity and specificity of 64.17 (±47.34) and 95.23% (±22.94), respectively.

Committee feedback

No Committee feedback was relevant to this evidence.

New evidence is unlikely to change guideline recommendations.

Q – 15 In people under investigation for asthma, what is the diagnostic accuracy of bronchoconstriction in response to an exercise challenge?

Recommendations derived from this question

26. Do not offer adults and young people older than 16 an exercise challenge test as a diagnostic test for asthma.

Update decision

No new information was identified.

Diagnostic test accuracy of bronchoconstriction

Update summary

No relevant evidence was identified.

Committee feedback

No Committee feedback was relevant to this evidence

Diagnostic algorithms

Recommendations derived from this question

Children younger than 5 years (algorithm A1)

27. Treat symptoms based on observation and clinical judgement in children younger than 5 years, and plan to review when they reach age 5 using the following criteria:
    - if the child still has symptoms, perform objective tests while on current treatment
    - if the child does not have symptoms on treatment, step down (and when appropriate, stop) treatment before performing objective tests.

    Review the diagnosis of asthma in children with normal test results.

Adults, young people and children aged 5 years and over (algorithm A2)

28. Do not diagnose asthma based on any single test alone in adults and children aged 5 years and over.

Adults and young people older than 16 with obstructive spirometry (algorithm B1)

29. Diagnose asthma in adults and young people older than 16 if they have obstructive spirometry and:
    - negative bronchodilator reversibility, a FeNO level between 25 and 39 ppb, negative peak flow variability and a positive direct bronchial challenge test **or**
    - positive bronchodilator reversibility and a FeNO level of 40 ppb or more **or**
    - positive bronchodilator reversibility, a FeNO level of 39 ppb or less and positive peak flow variability test **or**
    - positive bronchodilator reversibility, a FeNO level between 25 and 39 ppb, negative peak flow variability and a positive direct bronchial challenge test.

30. Suspect asthma in adults and young people older than 16 with obstructive spirometry, negative bronchodilator reversibility and:
    - a FeNO level of 40 ppb or more **or**
    - a FeNO level between 25 and 39 ppb and positive peak flow variability.

    Do not rule out other diagnoses if symptom control continues to remain poor after treatment. Review the diagnosis after 6-10 weeks by repeating spirometry and objective measures of asthma control and reviewing symptoms.

31. In adults and young people older than 16 with obstructive spirometry, positive bronchodilator reversibility, negative peak flow variability and a FeNO level less than 25 ppb and ongoing symptoms, consider:
    - alternative diagnoses **or**
    - referral for specialist opinion.

    Base the choice on the person's clinical history (for example whether they smoke, their age, weight, how fit they are) together with their objective test results.

32. Consider alternative diagnoses in adults and young people older than 16 with obstructive spirometry and:
    - negative bronchodilator reversibility and a FeNO level less than 25 ppb **or**
    - positive bronchodilator reversibility, a FeNO level between 25 and 39 ppb, negative peak flow variability and a negative direct bronchial challenge test.

Adults and young people older than 16 with normal spirometry (algorithm B2)

33. Diagnose asthma in adults and young people older than 16 if they have normal spirometry and:
    - a FeNO level of 40 ppb or more and positive peak flow variability **or**
    - a FeNO level of 40 ppb or more, negative peak flow variability and a positive direct bronchial challenge test **or**
    - a FeNO level of 39 ppb or less, positive peak flow variability and a positive direct bronchial challenge test.
34. Consider alternative diagnoses in adults and young people older than 16 if they have normal spirometry and:
    - a FeNO level of 39 ppb or less and negative peak flow variability **or**
    - a FeNO level of 39 ppb or less, positive peak flow variability and a negative direct bronchial challenge test **or**
    - a FeNO level of 40 ppb or more, negative peak flow variability and a negative direct bronchial challenge test.

Children aged 5-16 (algorithm C)

35. Diagnose asthma in children aged 5–16 if they have:
    - normal spirometry, a FeNO level of 35 ppb or more and positive peak flow variability **or**
    - obstructive spirometry and positive bronchodilator reversibility **or**
    - obstructive spirometry, negative bronchodilator reversibility, a FeNO level of 35 ppb or more and positive peak flow variability.
36. Refer children aged 5–16 for specialist assessment if they have obstructive spirometry, negative bronchodilator reversibility and a FeNO level of 34 ppb or less.
37. Suspect asthma in children aged 5–16 if they have:
    - normal spirometry, a FeNO level of 35 ppb or more and negative peak flow variability **or**
    - obstructive spirometry, negative bronchodilator reversibility, a FeNO level of 35 ppb or more and negative peak flow variability **or**
    - normal spirometry, a FeNO level of 34 ppb or less and positive peak flow variability.

    Do not rule out other diagnoses if symptom control continues to remain poor after treatment. Review the diagnosis after 6 weeks by repeating any abnormal tests and reviewing symptoms.
38. Consider alternative diagnoses and referral for specialist assessment in children aged 5–16 if they have normal spirometry, a FeNO level of 34 ppb or less and negative peak flow variability.

People diagnosed with asthma

39. Record the evidence that a person's diagnosis of asthma is based on in a single entry in their medical records, alongside the coded diagnostic entry.

Update decision

The diagnostic algorithms should not be updated.

Q – 16 In people with asthma, what is the clinical and cost-effectiveness of using symptom scores / diaries or validated questionnaires measuring symptom control (eg ACT, ACQ, CACT, RCP 3 questions) and / or health related quality of life (eg AQLQ, PAQLQ) to monitor asthma?

Recommendations derived from this question

40. Monitor asthma control at every review. If control is suboptimal:
    - confirm the person's adherence to prescribed treatment in line with recommendations 1.2.1, 1.2.2 and 1.2.3 in the NICE guideline on medicines adherence
    - review the person's inhaler technique
    - review if treatment needs to be changed
    - if relevant, ask about occupational asthma and/or other triggers.

41. Consider using a validated questionnaire (the Asthma Control Questionnaire or Asthma Control Test) to monitor asthma control in adults and young people older than 16.

Update decision

This review question should not be updated.

Questionnaires measuring symptom control

Update summary

A sub-study[6] of a multicentre randomised controlled trial comparing the Asthma APGAR System with the Asthma Control Test (ACT) was identified. The study included 209 children and young people aged 18 years or younger and 259 adults with physician-diagnosed asthma. Enrolled patients completed the ACT, the APGAR patient questionnaire, and the Asthma Quality of Life Questionnaire (AQLQ) at the time of enrolment and every 6 months thereafter for 2 years. Children-specific versions of AQLQ and ACT were used. The ACT and APGAR system were found to similarly assess asthma control in the study (overall agreement was 84.4%). Of the 468 patients included in the study, 306 patients were classified as not controlled. Seventy-three of the 306 uncontrolled patients had no daily medications.

Committee feedback

No Committee feedback was relevant to this evidence.

New evidence is unlikely to change guideline recommendations.

Q – 17 In people with asthma, what is the clinical and cost-effectiveness of using measures of pulmonary function assessing asthma control (for example, spirometry and peak expiratory flow) to monitor asthma?

Recommendations derived from this question

42. Monitor asthma control at each review in adults and children aged 5 years and over by measuring either spirometry (FEV_1) or peak flow.

Update decision

No new information was identified.

Pulmonary function assessing asthma control

Update summary

No relevant evidence was identified.

Committee feedback

No Committee feedback was relevant to this evidence

Q – 18 In people with asthma, what is the clinical and cost-effectiveness of using fractional exhaled nitric oxide (FeNO) measures for monitoring asthma control?

Recommendations derived from this question

43. Do not routinely use FeNO to monitor asthma control.
44. Consider FeNO measurement as an option to support asthma management in people who are symptomatic despite using inhaled corticosteroids. (This recommendation is from NICE's diagnostics guidance on measuring fractional exhaled nitric oxide concentration in asthma.)

Update decision

This review question should not be updated.

Clinical effectiveness of FeNO monitoring

Update summary

A randomised controlled trial[7] assessing the effectiveness of 4-monthly monitoring of FeNO and a web-based monthly monitoring strategy compared with standard care was identified. The study included 280 children with atopic asthma. The primary outcome was the change in symptom-free days at 1-year follow-up. There was no significant difference in change in the proportion of symptom-free days between the treatment arms. The proportion of symptom-free days decreased by 2.07% in the web-based group and increased by 8.90% and 7.40% in the FeNO and standard care groups, respectively. The mean difference between the web-based group and the standard care group was -6.60% and 1.17% between the FeNO group and the standard care group. There was a significant decrease in inhaled corticosteroid use in both the web-based and FeNO groups. The difference between treatment groups was only significant when comparing the web-based strategy with standard care. There was no significant difference in ACT scores.

Committee feedback

No Committee feedback was relevant to this evidence.

New evidence is unlikely to change guideline recommendations.

Cost-effectiveness of FeNO monitoring

Update summary

One economic evaluation[1] assessing the cost effectiveness of 4-monthly monitoring of FeNO and a web-based monthly monitoring strategy compared with standard care was identified. The economic evaluation is based on the randomised controlled trial[7] mentioned above. Two hundred and seventy-two children with asthma were randomised to one of the three treatment arms. Asthma control was assessed using the Asthma Control Test (ACT) and the health economic outcome was the cost per quality adjusted life years (QALY) gained. QALYs were calculated using the Dutch tariff of the EQ-5D. Assuming the cost year to be 2015, the total cost per patient per year for standard care, web-based monitoring and FeNO monitoring were €839 [£703], €924 [£774] and €837 [£701], respectively. At a generally acceptable willingness-to-pay threshold of €40,000 [£33,513] per QALY, the web-based strategy had a 77% chance of being most cost-effective from a healthcare perspective. FeNO monitoring and standard care had a chance of 3% and 20%, respectively, to be cost effective.

The probability of these interventions to be cost-effective at a £20,000/QALY threshold is therefore significantly lower than the one stated above.

Committee feedback

No Committee feedback was relevant to this evidence.

New evidence is unlikely to change guideline recommendations.

Q – 19 In people with asthma, what is the clinical and cost-effectiveness of using the peripheral blood eosinophil count for monitoring asthma control?

Recommendations derived from this question

No clinical recommendations.

Update decision

No new information was identified.

Blood eosinophil count

Update summary

No relevant evidence was identified.

Committee feedback

No Committee feedback was relevant to this evidence

Q – 20 In people with asthma, what is the clinical and cost-effectiveness of using indirect challenge tests with mannitol or direct challenge tests with histamine or methacholine for monitoring asthma control?

Recommendations derived from this question

45. Do not use challenge testing to monitor asthma control.

Update decision

No new information was identified.

Indirect challenge tests

Update summary

No relevant evidence was identified.

Committee feedback

No Committee feedback was relevant to this evidence

Direct challenge tests

Update summary

No relevant evidence was identified.

Committee feedback

No Committee feedback was relevant to this evidence

Q – 21 In people with asthma, what is the clinical and cost-effectiveness of monitoring adherence to treatment?

Recommendations derived from this question

No clinical recommendations.

Update decision

This review question should not be updated.

Adherence to treatment

Update summary

A randomised controlled trial[4] comparing an online tool designed to encourage patients to ask their provider questions about their asthma care with no monitoring of adherence was identified. The study included 407 adults with persistent asthma. Patients in the intervention group answered questions online about their asthma symptoms, medications and care at least once a month and received tailored reminders to ask their health care providers specific questions that may improve asthma control. Patients in the control group received questions on preventive services unrelated to asthma. At the 12-month follow-up patients in the intervention group reported a greater mean improvement in the Asthma Control Test (ACT) score than patients in the control group (2.3 versus 1.2; p=0.02). There were no differences in medication adherence, number of asthma controller medications or health care utilisation.

A randomised controlled trial[2] including 220 children aged 6-15 years with an asthma exacerbation was identified. Children received an electronic monitoring device for use with their preventer inhaler. Depending on whether a child was randomly allocated to the intervention or the control group, the audiovisual reminder functions were either enabled or disabled. Participants were followed up every 2 months for a total of 6 months. Adherence to treatment and number of days absent from school for any reason were the primary outcomes. Asthma control was assessed as a secondary outcome. Adherence to treatment was defined as the proportion of preventer doses taken relative to the number of doses prescribed. Adherence to treatment was found to be significantly better in the intervention group (median adherence 84%) than in the control group (median adherence 30%). The intervention group also had a significantly greater reduction in asthma morbidity score from baseline than the control group with a reduction of 2 points and 1.2 points, respectively. There was no difference in the proportion of days absent from school between the two groups.

Committee feedback

No Committee feedback was relevant to this evidence.

New evidence is unlikely to change guideline recommendations.

Q – 22 In people with asthma, what is the optimal frequency and method for monitoring inhaler technique?

Recommendations derived from this question

46. Observe and give advice on the inhaler technique of people with asthma:
    - at every consultation relating to an asthma attack, in all care settings
    - when there is deterioration in asthma control
    - when the device is changed
    - at every annual review
    - if the person asks for it to be checked.

Update decision

No new information was identified.

Inhaler technique

Update summary

No relevant evidence was identified.

Committee feedback

No Committee feedback was relevant to this evidence.

Q – 23 In people with asthma, what is the clinical and cost-effectiveness of tele-healthcare to monitor asthma control?

Recommendations derived from this question

No clinical recommendations.

Update decision

This review question should not be updated.

Tele-healthcare

Update summary

A randomised controlled trial[9] evaluated the efficacy of tele-healthcare in 72 pregnant women with asthma. Participants were either allocated to MASTERY, a programme using the COPD-6 device to measure lung function (forced expiratory volume in 6 seconds) daily and the Breathe-easy mobile phone app to record asthma symptoms and medications weekly, or a usual care group. Change in asthma control was measured by the Asthma Control Questionnaire (ACQ-7) and change in asthma-related quality of life was measured by the mini-Asthma Quality of Life Questionnaire (mAQLQ) at 3 and 6 months. At 6 months, patients in the MASTERY group had better asthma control and asthma-related quality of life than the usual care group. The mean difference was -0.36 (SD 0.15) on the ACQ and +0.72 (SD 0.22) on the mAQLQ.

A cluster-randomised trial[3] assessed the effectiveness of telephone peer coaching for parents on the reduction of asthma morbidity of their children. A total of 948 families were recruited, 462 of which received telephone peer coaching. The remaining 486 families were allocated to usual care. The intervention included repeated telephone conversations with a peer trainer to clarify the programme's goals, gain feedback from parents to assess if the goals had been reached and further tailored guidance. After 12 months, there were 20.9 (95% CI, 9.1-32.7) more symptom-free days per child in the telephone peer coaching group than in the usual care group. After 24 months, children in the telephone peer coaching group had on average 0.28 fewer emergency department visits than children in the control group. There was no difference in emergency department visits at 12 months, indicating a delayed treatment effect.

Committee feedback

No Committee feedback was relevant to this evidence.

New evidence is unlikely to change guideline recommendations.

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